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(54) Title: UREA DERIVATIVES

(57) Abstract: This invention relates to urea derivatives and salts thereof which is useful as an active ingredient of pharmaceutical preparations. The urea derivatives of the present invention has an excellent activity as VR1 antagonist and useful for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of urge urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence and/or inflammatory disorders.

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UREA DERIVATIVES

DETAILED DESCRIPTION OF INVENTION

TECHNICAL FIELD

The present invention relates to an urea derivative, which is useful as an active ingredient of pharmaceutical preparations. The urea derivatives of the present invention have vanilloid receptor (VR1) antagonistic activity, and can be used for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of urge urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence and/or inflammatory disorders.

BACKGROUND ART

Vanilloid compounds are characterized by the presence of vanillyl group or a functionally equivalent group. Examples of several vanilloid compounds or vanilloid receptor modulators are vanillin (4-hydroxy-3-methoxy-benzaldehyde), guaiacol (2-methoxy-phenol), zingerone (4-/4-hydroxy-3-methoxyphenyl/-2-butanon), eugenol(2-methoxy4-/2-propenyl/phenol), and capsaicin (8-methy-N-vanillyl-6-noneneamide).

Among others, capsaicin, the main pungent ingredient in "hot" chili peppers, is a specific neurotoxin that desensitizes C-fiber afferent neurons. Capsaicin interacts with vanilloid receptors (VR1), which are predominantly expressed in cell bodies of dorsal root ganglia (DRG) or nerve endings of afferent sensory fibers including C-fiber nerve endings [Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, Raumann BE, Basbaum AI, Julius D: The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron. 21: 531-543, 1998]. The VR1

receptor was recently cloned [Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D: Nature 389: 816-824, (1997)] and identified as a nonselective cation channel with six transmembrane domains that is structurally related to the TRP (transient receptor potential) channel family. Binding of capsaicin to VR1 allows sodium, calcium and possibly potassium ions to flow down their concentration gradients, causing initial depolarization and release of neurotransmitters from the nerve terminals. VR1 can therefore be viewed as a molecular integrator of chemical and physical stimuli that elicit neuronal signals in a pathological conditions or diseases.

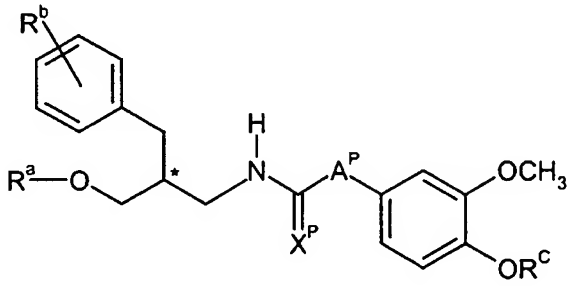
There are abundant of direct or indirect evidence that shows the relation between VR1 activity and diseases such as pain, ischaemia, and inflammatory (e.g., WO 99/00115 and 00/50387). Further, it has been demonstrated that VR1 transduce reflex signals that are involved in the overactive bladder of patients who have damaged or abnormal spinal reflex pathways [De Groat WC: A neurologic basis for the overactive bladder. Urology 50 (6A Suppl): 36-52, 1997]. Desensitisation of the afferent nerves by depleting neurotransmitters using VR1 agonists such as capsaicin has been shown to give promising results in the treatment of bladder dysfunction associated with spinal cord injury and multiple sclerosis [(Maggi CA: Therapeutic potential of capsaicin-like molecules - Studies in animals and humans. Life Sciences 51: 1777-1781, 1992) and (DeRidder D; Chandiramani V; Dasgupta P; VanPoppel H; Baert L; Fowler CJ: Intravesical capsaicin as a treatment for refractory detrusor hyperreflexia: A dual center study with long-term followup. J. Urol. 158: 2087-2092, 1997)].

It is anticipated that antagonism of the VR1 receptor would lead to the blockage of neurotransmitter release, resulting in prophylaxis and treatment of the condition and diseases associated with VR1 activity.

It is therefore expected that antagonists of the VR1 receptor can be used for prophylaxis and treatment of the condition and diseases including chronic pain,

neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence, inflammatory disorders, urge urinary incontinence (UUI), and/or overactive bladder.

WO 2000/50387 discloses the compounds having a vanilloid agonist activity represented by the general formula:



wherein;

X^P is an oxygen or sulfur atom;

A^P is $-NHCH_2-$ or $-CH_2-$;

R^a is a substituted or unsubstituted C_{1-4} alkyl group, or $R^{a1}CO-$;

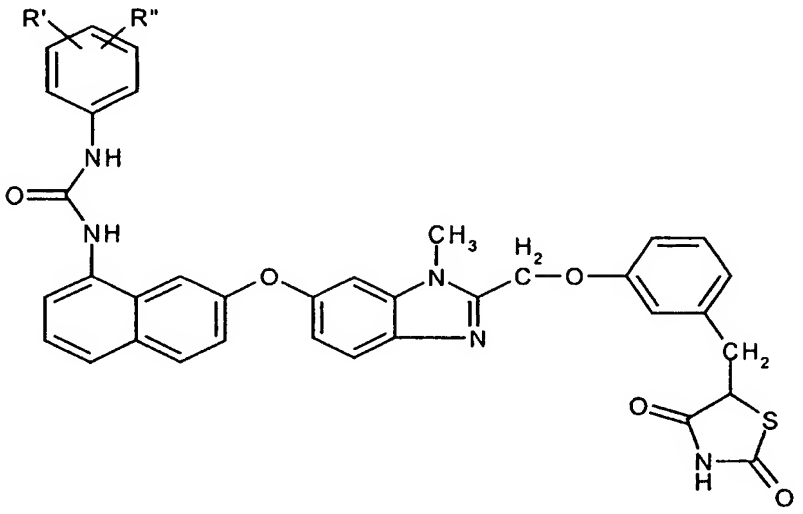
wherein R^{a1} is an alkyl group having 1 to 18 carbon atoms, an alkenyl group having 2 to 18 carbon atoms, or substituted or unsubstituted aryl group having 6 to 10 carbon atoms;

R^b is a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, an alkoxy group having 1 to 6 carbon atoms, a haloalkyl group having 1 to 6 carbon atoms or a halogen atom;

R^C is a hydrogen atom, an alkyl group having 1 to 4 carbon atom, an aminoalkyl, a diacid monoester or .-alkyl acid; and

the asteric mark * indicates a chiral carbon atom, and their pharmaceutically acceptable salts.

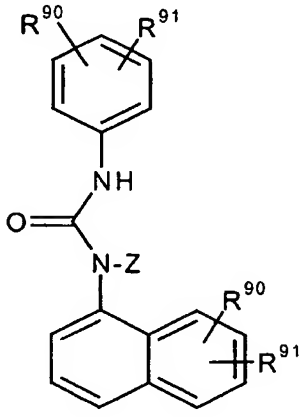
WO 2000/61581 discloses amine derivatives represented by the general formula:



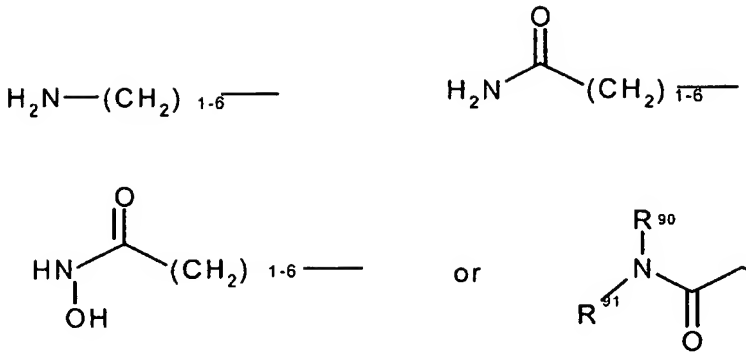
wherein (R', R") represent (F, F), (CF_3, H), or (iPr, iPr)

as useful agents for diabetes, hyperlipemia, arteriosclerosis and cancer.

WO 2000/75106 discloses the compounds represented by the general formula:



wherein Z represents



in which R^{90} is hydrogen, C_{1-12} alkyl, C_{3-8} cycloalkyl, or the like, and R^{91} is amino-C_{1-6} alkyl, aminocarbonyl-C_{1-6} alkyl, or hydroxyaminocarbonyl C_{1-6} alkyl; and

R^{90} and R^{91} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkylthio, C_{1-6} alkoxy, fluoro, chloro, bromo, iodo, and nitro;

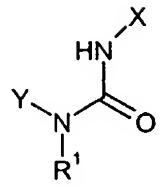
as useful agents for treating MMP-mediated diseases in mammals.

However, none of these reference discloses simple urea derivatives having pharmaceutical activity.

The development of a compound having effective VR1 antagonistic activity and the use of such compound for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of urge urinary incontinence and/or overactive bladder have been desired.

SUMMARY OF THE INVENTION

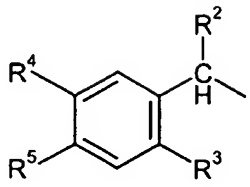
This invention is to provide urea derivatives of the formula (I), their tautomeric and stereoisomeric form, and salts thereof:



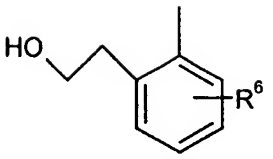
(I)

wherein

Y is



(I-i) or



(I-ii) ;

X is C_{1-6} alkyl substituted by phenyl or naphthyl (wherein said phenyl and naphthyl are optionally substituted by R^{11}, R^{12} and R^{13}), aryl or heterocyclic ring ,

wherein said aryl and heterocyclic ring are optionally substituted by R^{11}, R^{12} and R^{13} and are selected from the group consisting of phenyl, naphthyl, pyridyl, carbazolyl, fluorenyl, thienyl, pyrimidyl, benzodioxolyl, indazolyl, and quinolyl,

in which R^{11}, R^{12} and R^{13} independently represent hydrogen, halogen, C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyl, nitro, cyano, C_{1-6} alkoxy, hydroxy, piperidino, furyl, thienyl, benzyloxy, anilino, naphthyl, C_{1-6} alkylcarbamoyl, carbamoyl, carboxyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} alkoxy-carbonyl, benzyl, phenoxy, C_{1-6} alkyl substituted phenoxy, pyridyl, halogen substituted phenoxy, C_{1-6} alkylthio, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, hydroxy substituted C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyloxy, or phenyl optionally substituted by one to three substituents,

in which the substituents are each different or identical and selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, pyridyl, mono-, di-, or tri-halogen substituted C_{1-6} alkyl, nitro, cyano, benzyloxy, thienyl, C_{1-6}alkanoyl, C_{1-6}

alkoxycarbonyl, C_{1-6} alkylthio, di(C_{1-6} alkyl)amino, and C_{1-6} alkylamino, mono, di, or tri halogen substituted C_{1-6} alkyloxy;

R^1 is hydrogen,

R^2 is hydrogen,

R^3 is hydrogen,

or

R^2 and R^3 together form $-(CH_2)_m-$ (wherein m represents 1, 2, 3 or 4),

or

R^1 and R^3 together form $-(CH_2)_n-$ (wherein n represents 1, 2, or 3);

R^4 is hydrogen, halogen, C_{1-6} alkoxy, hydroxy, C_{1-6} alkoxy substituted benzyloxy, sulfamoyl, C_{1-6} alkylsulfamoyl, di(C_{1-6} alkyl)sulfamoyl, di (C_{1-6} alkyl)aminoC_{1-6} alkylene sulfamoyl, hydroxy C_{1-6} alkyl piperazinosulfonyl, C_{1-6} alkylsulfonylamino, nitro, amino, C_{1-6} alkanoylamino, C_{1-6} alkoxyC_{1-6} alkyleneoxy,

R^5 is hydrogen, halogen, C_{1-6} alkoxy, hydroxy, C_{1-6} alkoxy substituted benzyloxy, sulfamoyl, C_{1-6} alkylsulfamoyl, di (C_{1-6} alkyl)sulfamoyl, di(C_{1-6} alkyl)amino C_{1-6}alkylene sulfamoyl, hydroxy C_{1-6} alkyl piperazinosulfonyl, C_{1-6} alkylsulfonylamino, nitro, amino, C_{1-6} alkanoylamino, C_{1-6} alkoxyC_{1-6} alkyleneoxy,

or

R^4 and R^5 together form $-O-(CH_2)-O-$; and

R^6 is hydrogen, halogen, C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyl, nitro, cyano, C_{1-6} alkoxy, hydroxy, C_{1-6} alkylcarbamoyl, carbamoyl, carboxyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl) amino, C_{1-6} alkoxycarbonyl, phenyl, benzyl, phenoxy, halogen substituted phenoxy, C_{1-6} alkylthio, C_{1-6}

alkanoyl, C_{1-6} alkanoylamino, hydroxy substituted C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkoxy.

The urea derivatives of formula (I), their tautomeric and stereoisomeric form, and salts thereof surprisingly show excellent VR1 antagonistic activity. They are, therefore suitable especially for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of urge urinary incontinence and/or overactive bladder.

Alkyl per se and "alk" and "alkyl" in alkoxy, alkanoyl, alkylthio, alkylamino, alkylaminocarbonyl, alkylaminosulphonyl, alkylsulphonylamino, alkoxycarbonyl, alkoxycarbonylamino, alkylcarbamoyl and alkanoylamino represent a linear or branched alkyl radical having generally 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3 carbon atoms, representing illustratively and preferably methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl and n-hexyl.

Alkoxy illustratively and preferably represents methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

Alkanoyl illustratively and preferably represents acetyl and propanoyl.

Alkylamino represents an alkylamino radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexyl-amino, N,N-dimethylamino, N,N-diethylamino, N-ethyl-N-methylamino, N-methyl-N-n-propylamino, N-isopropyl-N-n-propylamino, N-t-butyl-N-methylamino, N-ethyl-N-n-pentylamino and N-n-hexyl-N-methylamino.

Alkylaminocarbonyl or alkylcarbamoyl represents an alkylaminocarbonyl radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylaminocarbonyl, ethylaminocarbonyl, n-propylamino-

carbonyl, isopropylamino-carbonyl, tert-butylaminocarbonyl, n-pentylamino-carbonyl, n-hexylaminocarbonyl, N,N-dimethylaminocarbonyl, N,N-diethylamino-carbonyl, N-ethyl-N-methylaminocarbonyl, N-methyl-N-n-propylaminocarbonyl, N-isopropyl-N-n-propylaminocarbonyl, N-t-butyl-N-methylaminocarbonyl, N-ethyl-N-n-pentylamino-carbonyl and N-n-hexyl-N-methylaminocarbonyl.

Alkoxycarbonyl illustratively and preferably represents methoxycarbonyl, ethoxy-carbonyl, n-propoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, n-pentoxy-carbonyl and n-hexoxycarbonyl. Alkoxycarbonylamino illustratively and preferably represents methoxycarbonylamino, ethoxycarbonylamino, n-propoxycarbonylamino, isopropoxycarbonylamino, tert-butoxycarbonylamino, n-pentoxycarbonylamino and n-hexoxycarbonylamino.

Alkanoylamino illustratively and preferably represents acetylamino and ethyl-carbonylamino.

Halogen represents fluorine, chlorine, bromine and iodine.

Aryl per se and in arylamino and in arylcarbonyl represents a mono- to tricyclic aromatic carbocyclic radical having generally 6 to 14 carbon atoms, and more preferably from 6-10 carbon atoms, optionally substituted with one or more substituents. Examples of aryl radicals include, but are not limited to phenyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, biphenyl, fluorenonyl and the like.

Heterocyclic ring refers to a 3- to 15-membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. The heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems and may be partially or fully saturated or aromatic. Examples of such rings include, but are not limited to thienyl, benzothienyl, furanyl, benzofuranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, isothiazolyl, thiazolyl,

oxazolyl, isoxazolyl, triazolyl, tetrazolyl, imidazolyl, thiadiazolyl, benzothiadiazolyl, oxadiazolyl, benzothiazolyl, indolyl, carbazolyl, quinolinyl, isoquinolinyl, benzodioxolyl, indazolyl, indazolinolyl and the like

This invention is also to provide a method for treating or preventing a disorder or disease associated with VR1 activity in a human or animal subject, comprising administering to said subject a therapeutically effective amount of the urea derivative shown in the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof.

Further this invention is to provide a use of the urea derivative shown in the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof in the preparation of a medicament. Preferably, said medicament is suitable for treating or preventing a disorder or disease associated with VR1 activity.

The compounds of the present invention surprisingly show excellent VR1 activity. They are, therefore, suitable for the production of medicament or medical composition, which may be useful to treat VR1 related diseases.

More specifically, since the urea derivatives of the present invention inhibit VR1 , they are useful for treatment and prophylaxis of diseases as follows:

urinary incontinence, overactive bladder, chronic pain, neuropathic pain, post-operative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence and inflammatory disorders

In one embodiment, the compounds of formula (I) are those wherein:

Y is I-i;

X is phenyl optionally substituted by R^{11}, R^{12} and R^{13}, phenyl C_{1-6} alkyl (wherein said phenyl is optionally substituted by R^{11}, R^{12} and R^{13}), or naphthyl optionally substituted by R^{11}, R^{12} and R^{13},

in which R^{11}, R^{12} and R^{13} independently represent hydrogen, halogen, C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyl, nitro, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, phenoxy, C_{1-6} alkylthio, or C_{1-6} alkanoyl.

In another embodiment, the compounds of formula (I) are those wherein:

Y is I-i;

R^1 is hydrogen;

R^2 is hydrogen; and

R^3 is hydrogen.

In another embodiment, the compounds of formula (I) are those wherein:

Y is I-i;

X is phenyl optionally substituted by R^{11}, R^{12} and R^{13}, phenyl C_{1-6} alkyl (wherein said phenyl is optionally substituted by R^{11}, R^{12} and R^{13}), or naphthyl optionally substituted by R^{11}, R^{12} and R^{13},

in which R^{11}, R^{12} and R^{13} independently represent hydrogen, halogen, C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyl, nitro, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, phenoxy, C_{1-6} alkylthio, or C_{1-6} alkanoyl.

R^1 is hydrogen; and

R^2 and R^3 together form $-(CH_2)_m-$ (wherein m represents 1, 2, 3 or 4).

In another embodiment, the compounds of formula (I) are those wherein:

Y is I-i;

R^1 and R^3 together form $-(CH_2)_n-$ (wherein n represents 1, 2, or 3) and

R^2 is hydrogen.

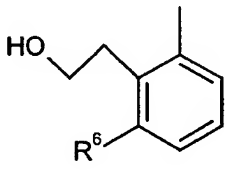
alternatively, the urea derivative of formula (I) can be those wherein:

Y is I-ii;

R^6 is hydrogen, halogen, C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyl, phenyl, or C_{1-6} alkoxy.

In another embodiment, the compounds of formula (I) are those wherein:

Y is



(I-ii-a);

X is C_{1-6} alkyl substituted by phenyl or naphthyl (wherein said phenyl and naphthyl are optionally substituted by R^{11}, R^{12} and R^{13}), aryl or Heterocyclic ring ,

wherein said aryl and Heterocyclic ring are optionally substituted by R^{11}, R^{12} and R^{13} and are selected from the group consisting of phenyl, naphthyl,

pyridyl, carbazolyl, fluorenyl, thienyl, benzodioxolyl, indazolyl, and quinolyl,

R^6 is hydrogen, halogen, C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyl, phenyl, or C_{1-6} alkoxy.

The preferable compounds of the present invention are as follows:

N-(4-hydroxy-3-methoxybenzyl)-N'-(4-isopropylphenyl)urea;
N-(4-hydroxy-3-methoxybenzyl)-N'-(1-naphthyl)urea;
N-(3,4-dichlorophenyl)-N'-(4-hydroxy-3-methoxybenzyl)urea;
N-(3-chloro-4-methylphenyl)-N'-(4-hydroxy-3 methoxybenzyl)urea;
N-(4-hydroxy-3-methoxybenzyl)-N'-(4-phenoxyphenyl)urea;
N-[2-chloro-5-(trifluoromethyl)phenyl]-N'-(4-hydroxy-3-methoxybenzyl)urea;
N-(3-chlorophenyl)-N'-(4-hydroxy-3-methoxybenzyl)urea;
N-(4-chlorophenyl)-N'-(4-hydroxy-3-methoxybenzyl)urea;
N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-hydroxy-3-methoxybenzyl)urea;
N-(4'-chloro-1,1'-biphenyl-3-yl)-N'-(4-hydroxy-3-metoxybenzyl)urea;
N-[2-(2-hydroxyethyl)phenyl]-N'-[4'-(methylsulfanyl)-1,1'-biphenyl-3-yl]urea;
N-[2-(2-hydroxyethyl)phenyl]-N'-(4'-nitro-1,1'-biphenyl-3-yl)urea;
N-(4'-acetyl-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
Ethyl3'-[({[2-(2hydroxyethyl)phenyl]amino}carbonyl)amino]-1,1'-biphenyl-4-carboxylate;
N-[2-(2-hydroxyethyl)phenyl]-N'-[2'-(trifluoromethyl)-1,1'-biphenyl-3-yl]urea;
N-(2'-chloro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-[2-(2-hydroxyethyl)phenyl]-N'-[3-(1-naphthyl)phenyl]urea;

N-[2-(2-hydroxyethyl)phenyl]-N'-[4'-(trifluoromethyl)-1,1'-biphenyl-3-yl]urea;
N-(4',6-dichloro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-(2',5'-dichloro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-(2',4'-dichloro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-(3',4'-difluoro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-(4'-fluoro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-[2-(2-hydroxyethyl)phenyl]-N'-(3'-nitro-1,1'-biphenyl-3-yl)urea;
N-[4'-(benzyloxy)-3'-fluoro-1,1'-biphenyl-3-yl]-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-(4'-chloro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-(2',5'-dimethyl-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-[2-(2-hydroxyethyl)phenyl]-N'-[4'-(trifluoromethoxy)-1,1'-biphenyl-3-yl]urea;
N-(4'-chloro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)-3-methoxyphenyl]urea;
N-(3'-fluoro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-(3'-chloro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-(2',5'-difluoro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea; and
N-(3'-chloro-4'-fluoro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea.

Preferably, the medicaments of the present invention further comprise one or more pharmaceutically acceptable carrier and/or excipients.

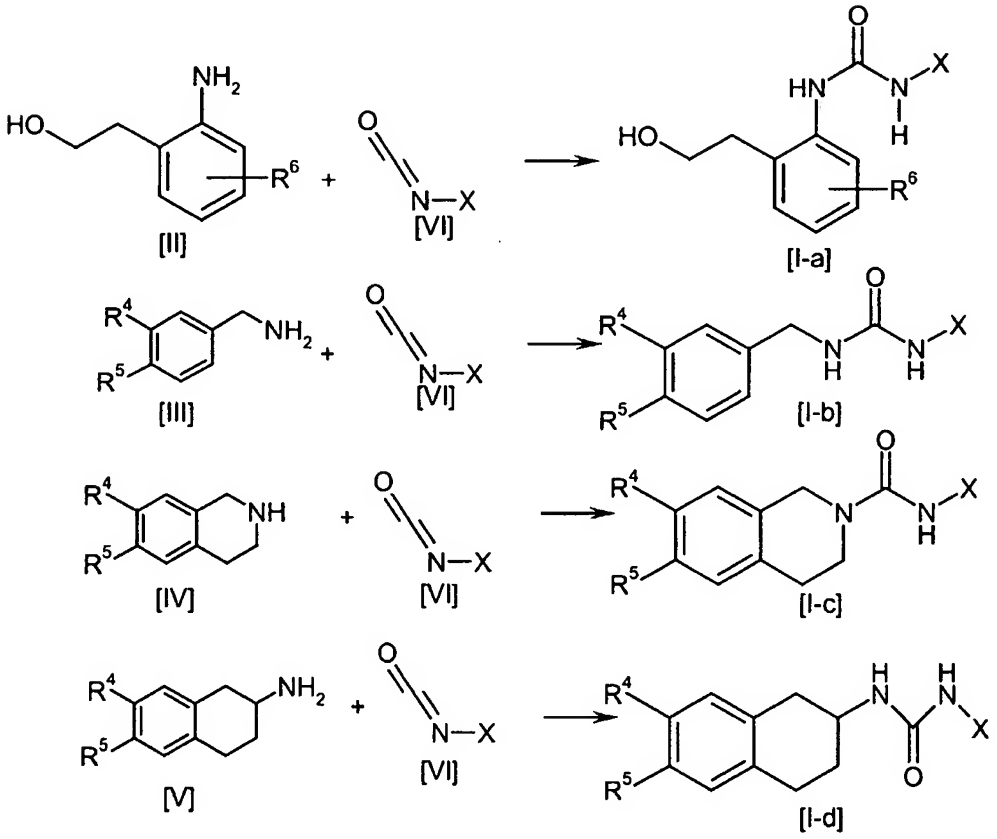
EMBODIMENT OF THE INVENTION

The compound of the formula (I) of the present invention can be, but not limited to be, prepared by either of the methods [A], [B] and [C] below. In some embodiments, one or more of the substituents, such as amino group, carboxyl group, and hydroxyl group of the compounds used as starting materials or intermediates are ad-

vantageously protected by a protecting group known to those skilled in the art. Examples of the protecting groups are described in

"Protective Groups in Organic Synthesis (3rd Edition)" by Greene and Wuts, John Wiley and Sons, New York 1999.

[Method A]



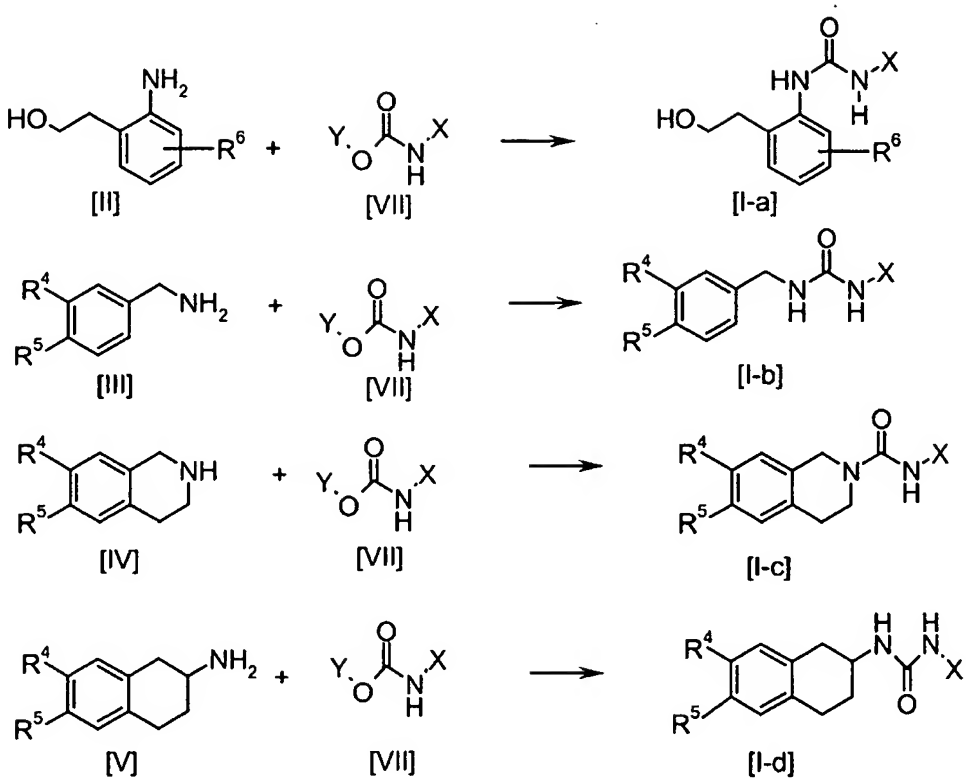
The compound [I-a] wherein X and R^6 are the same as defined above, can be prepared by the reaction of a substituted 2-(2-aminophenyl)ethanol[II] (wherein R^6 is the same as defined above) and isocyanate of the formula [VI] (wherein X is the same as defined above).

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 30 °C to 100 °C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

The compound [I-b], [I-c] and [I-d] wherein X, R^4 and R^5 are the same as defined above, can be prepared using substituted benzylamines [III], substituted tetrahydro-isoquinolines [IV] and substituted tetrahydro-naphthalenylamine [V] as starting material, respectively, by the same method as for the compound [I-a].

[Method B]



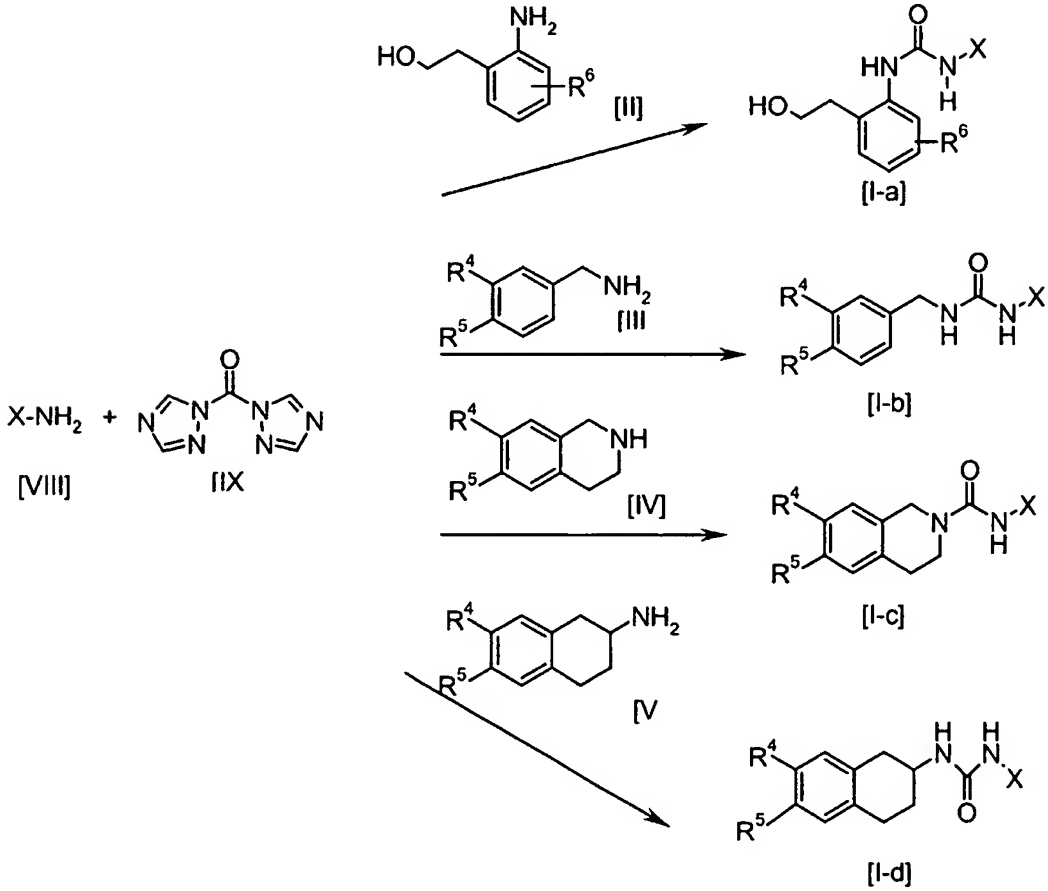
Alternatively, the compound [I-a] (wherein X and R^6 are the same as defined above) can be prepared by reacting a substituted 2-(2-aminophenyl)ethanol[II] and carbamate of the formula [VII] (wherein X is the same as defined above and Y represents phenyl).

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone(NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20 °C to 100 °C. The reaction may be conducted for, usually, 30 minutes to 40 hours and preferably 1 to 24 hours.

The compound [I-b], [I-c] and [I-d] wherein X, R^4 and R^5 are the same as defined above, can be prepared using substituted benzylamines [III], substituted tetrahydro-isoquinolines [IV] and substituted tetrahydro-naphthalenylamine [V] as starting material, respectively, by the same method as for the compound [I-a].

[Method C]



The compound [I-a] can be prepared by reacting amine of the formula [VIII](wherein X is the same as defined above) and 1,1'-carbonyldi(1,2,4-triazole) (CDT)[IX], and

then adding substituted 2-(2-aminophenyl)ethanol[II] to the reaction mixture. The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide(DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone(DMI); sulfoxides such as dimethylsulfoxide(DMSO); and others.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20 °C to 50 °C. The reaction may be conducted for, usually, 30 minutes to 10 hours and preferably 1 to 24 hours.

The compound [I-b], [I-c] and [I-d] wherein X, R^4 and R^5 are the same as defined above, can be prepared using substituted benzylamines [III], substituted tetrahydro-isoquinolines [IV] and substituted tetrahydro-naphthalenylamine [V] as starting material, respectively, by the same method as for the compound [I-a].

The substituted 2-(2-aminophenyl)ethanols [II], substituted benzylamines [III], substituted tetrahydroisoquinolines [IV], substituted tetrahydro-naphthalenylamine [V], Isocyanates [VI], carbamates [VII], amine [VIII] and CDT [IX] are commercially available or can be prepared by the use of known techniques or by method described in the examples.

When the compound shown by the formula (I) or a salt thereof has tautomeric isomers and/or stereoisomers (e.g., geometrical isomers and conformational isomers), each of their separated isomer and mixtures are also included in the scope of the present invention.

When the compound shown by the formula (I) or a salt thereof has an asymmetric carbon in the structure, their optically active compounds and racemic mixtures are also included in the scope of the present invention.

Typical salts of the compound shown by the formula (I) include salts prepared by reaction of the compounds of the present invention with a mineral or organic acid, or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively.

Acids to form acid addition salts include inorganic acids such as, without limitation, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydriodic acid and the like, and organic acids, such as, without limitation, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

Base addition salts include those derived from inorganic bases, such as, without limitation, ammonium hydroxide, alkaline metal hydroxide, alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, and organic bases, such as, without limitation, ethanolamine, triethylamine, tris(hydroxymethyl)aminomethane, and the like. Examples of inorganic bases include, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

The compound of the present invention or a salts thereof, depending on its substituents, may be modified to form lower alkylesters or known other esters; and/or hydrates or other solvates. Those esters, hydrates, and solvates are included in the scope of the present invention.

The compound of the present invention may be administered in oral forms, such as, without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols

and emulsions. They may also be administered in parenteral forms, such as, without limitation, intravenous, intraperitoneal, subcutaneous, intramuscular, and the like forms, well-known to those of ordinary skill in the pharmaceutical arts. The compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well-known to those of ordinary skilled in the art.

The dosage regimen with the use of the compounds of the present invention is selected by one of ordinary skill in the arts, in view of a variety of factors, including, without limitation, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed.

The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically-acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Yet another embodiment of the present invention is pharmaceutical formulation comprising a compound of the invention and one or more pharmaceutically-acceptable excipients that are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical formulations of the invention are prepared by combining a therapeutically effective amount of the compounds of the invention together with one or more pharmaceutically-acceptable excipients therefore. In making the compositions of the present invention, the active ingredient may be mixed with a diluent, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper, or other container. The carrier may serve as a diluent, which may be solid, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills powders, lozenges, elixirs, suspensions, emulsions,

solutions, syrups, aerosols, ointments, containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

For oral administration, the active ingredient may be combined with an oral, and non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, sodium carbonate, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, methyl cellulose, and the like; together with, optionally, disintegrating agents, such as, without limitation, maize, starch, methyl cellulose, agar, bentonite, xanthan gum, alginic acid, and the like; and optionally, binding agents, for example, without limitation, gelatin, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like.

In powder forms, the carrier may be a finely divided solid which is in admixture with the finely divided active ingredient. The active ingredient may be mixed with a carrier having binding properties in suitable proportions and compacted in the shape and size desired to produce tablets. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel composition of the present invention. Suitable solid carriers are magnesium carboxy-methyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The formulation may be in unit dosage form, which is a physically discrete unit containing a unit dose, suitable for administration in human or other mammals. A unit dosage form can be a capsule or tablets, or a number of capsules or tablets. An "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

Typical oral dosages of the present invention, when used for the indicated effects, will range from about 0.01mg /kg/day to about 100 mg/kg/day, preferably from 0.1 mg/kg/day to 30 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 10 mg/kg/day. In the case of parenteral administration, it has generally proven advantageous to administer quantities of about 0.001 to 100mg /kg/day, preferably from 0.01 mg/kg/day to 1 mg/kg/day. The compounds of the present invention may be administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

EXAMPLES

The present invention will be described as a form of examples, but they should by no means be construed as defining the metes and bounds of the present invention.

In the examples below, all quantitative data, if not stated otherwise, relate to percentages by weight.

Mass spectra were obtained using electrospray (ES) ionization techniques (micro-mass Platform LC). Melting points are uncorrected. Liquid Chromatography - Mass spectroscopy (LC-MS) data were recorded on a Micromass Platform LC with Shimadzu Phenomenex ODS column(4.6 mm X 30 mm) flushing a mixture of acetonitrile-water (9:1 to 1:9) at 1 ml/min of the flow rate. TLC was performed on a precoated silica gel plate (Merck silica gel 60 F-254). Silica gel (WAKO-gel C-200 (75-150 μm)) was used for all column chromatography separations. All chemicals were reagent grade and were purchased from Sigma-Aldrich, Wako pure chemical industries, Ltd., Tokyo kasei kogyo co. Ltd., Arch corporation.

The effect of the present compounds were examined by the following assays and pharmacological tests.

[Measurement of capsaicin-induced Ca^{2+} influx in the human VR1-transfected CHO cell line] (Assay 1)

(1) Establishment of the human VR1-CHOluc9aeq cell line

Human vanilloid receptor (hVR1) cDNA was cloned from libraries of axotomized dorsal root ganglia (WO2000/29577). The cloned hVR1 cDNA was constructed with pcDNA3 vector and transfected into a CHOluc9aeq cell line. The cell line contains aequorin and CRE-luciferase reporter genes as read-out signals. The transfectants were cloned by limiting dilution in selection medium (DMEM/F12 medium (Gibco BRL) supplemented with

10% FCS, 1.4 mM Sodium pyruvate, 20 mM HEPES, 0.15% Sodium bicarbonate, 100 U/ml penicillin, 100 μg/ml streptomycin, 2 mM glutamine, non-essential amino acids and 2 mg/ml G418). Ca^{2+} influx was examined in the capsaicin-stimulated clones. A high responder clone was selected and used for further experiments in the project. The human VR1-CHOluc9aeq cells were maintained in the selection medium and passaged every 3-4 days at 1-2.5x10^5 cells/flask (75 mm^2).

(2) Measurement of Ca^{2+} influx using FDSS-3000

Human VR1-CHOluc9aeq cells were suspended in a culture medium which is the same as the selection medium except for G418 and seeded at a density of 1,000 cells per well into 384-well plates (black walled clear-base / Nalge Nunc International). Following the culture for 48 hrs the medium was changed to 2 μM Fluo-3 AM (Molecular Probes) and 0.02% Puronic F-127 in assay buffer (Hank's balanced salt solution (HBSS), 17 mM HEPES (pH7.4), 1 mM Probenecid, 0.1% BSA) and the cells were incubated for 60 min at 25°C. After washing twice with assay buffer the cells were incubated with a test compound or vehicle for 20 min at 25°C. Mobilization of cytoplasmic Ca^{2+} was measured by FDSS-3000 (λ_{ex}=488nm, λ_{em}=540nm / Hamamatsu Photonics) for 60 sec after the stimulation with 10 nM capsaicin. Integral R was calculated and compared with controls.

[Measurement of the capsaicin-induced Ca^{2+} influx in primary cultured rat dorsal root ganglia neurons] (Assay 2)

(1) Preparation of rat dorsal root ganglia neurons

New born Wister rats (5-11 days) were sacrificed and dorsal root ganglia (DRG) was removed. DRG was incubated with 0.1% trypsin (Gibco BRL) in PBS(-) (Gibco BRL) for 30 min at 37°C, then a half volume of fetal calf serum (FCS) was added and the cells were spun down. The DRG neuron cells

were resuspended in Ham F12/5% FCS/5% horse serum (Gibco BRL) and dispersed by repeated pipetting and passing through 70 μm mesh (Falcon). The culture plate was incubated for 3 hrs at 37°C to remove contaminating Schwann cells. Non-adherent cells were recovered and further cultured in laminin-coated 384 well plates (Nunc) at $1x10^4$ cells/50 μl/well for 2 days in the presence of 50 ng/ml recombinant rat NGF (Sigma) and 50 μM 5-fluoro-deoxyuridine (Sigma).

(2) Ca^{2+} mobilization assay

DRG neuron cells were washed twice with HBSS supplemented with 17 mM HEPES (pH 7.4) and 0.1% BSA. After incubating with 2 μM fluo-3AM (Molecular Probe), 0.02% PF127 (Gibco BRL) and 1 mM probenecid (Sigma) for 40 min at 37°C, cells were washed 3 times. The cells were incubated with VR1 antagonists or vehicle (dimethylsulphoxide) and then with 1 μM capsaicin in FDSS-6000 (λ_{ex}=480nm, λ_{em}=520nm / Hamamatsu Photonics). The fluorescence changes at 480nm were monitored for 2.5 min. Integral R was calculated and compared with controls.

[Organ bath assay to measure the capsaicin-induced bladder contraction] (Assay 3)

Male Wistar rats (10 week old) were anesthetized with ether and sacrificed by dislocating the necks. The whole urinary bladder was excised and placed in oxygenated Modified Krebs-Henseleit solution (pH 7.4) of the following composition (112mM NaCl, 5.9mM KCl, 1.2mM $MgCl_2$, 1.2mM NaH_2PO_4, 2mM $CaCl_2$, 2.5mM $NaHCO_3$, 12mM glucose). Contractile responses of the urinary bladder were studied as described previously [Maggi CA et al: Br.J.Pharmacol. 108: 801-805, 1993]. Isometric tension was recorded under a load of 1 g using longitudinal strips of rat detrusor muscle. Bladder strips were equilibrated for 60 min before each stimulation. Contractile response to 80 mM KCl was determined at 15 min intervals until reproducible responses were obtained. The response to KCl was used as an

internal standard to evaluate the maximal response to capsaicin. The effects of the compounds were investigated by incubating the strips with compounds for 30 min prior to the stimulation with 1 μM capsaicin (vehicle: 80% saline, 10% EtOH, and 10% Tween 80). One of the preparations made from the same animal was served as a control while the others were used for evaluating compounds. Ratio of each capsaicin-induced contraction to the internal standard (i.e. KCl-induced contraction) was calculated and the effects of the test compounds on the capsaicin-induced contraction were evaluated.

[Measurement of Ca^{2+} influx in the human P2X1-transfected CHO cell line]

(1) Preparation of the human P2X1-transfected CHOluc9aeq cell line

Human P2X1-transfected CHOluc9aeq cell line was established and maintained in Dulbecco's modified Eagle's medium (DMEM/F12) supplemented with 7.5% FCS, 20 mM HEPES-KOH (pH 7.4), 1.4 mM sodium pyruvate, 100 U/ml penicillin, 100 μg/ml streptomycin, 2 mM glutamine (Gibco BRL) and 0.5 Units/ml apyrase (grade I, Sigma). The suspended cells were seeded in each well of 384-well optical bottom black plates (Nalge Nunc International) at 3 x 10^3 / 50 μl / well. The cells were cultured for following 48 hrs to adhere to the plates.

(2) Measurement of the intracellular Ca^{2+} levels

P2X1 receptor agonist-mediated increases in cytosolic Ca^{2+} levels were measured using a fluorescent Ca^{2+} chelating dye, Fluo-3 AM (Molecular Probes). The plate-attached cells were washed twice with washing buffer (HBSS, 17 mM HEPES-KOH (pH 7.4), 0.1% BSA and 0.5 units/ml apyrase), and incubated in 40 μl of loading buffer (1 μM Fluo-3 AM, 1 mM probenecid, 1 μM cyclosporin A, 0.01% pluronic (Molecular Probes)in washing buffer) for 1 hour in a dark place. The plates were washed twice with 40 μl washing buffer and 35 μl of washing buffer were added in each well with 5 μl of test compounds or *2',3'-o*-(2,4,6-trinitrophenyl) adenosine 5'-

triphpsphate (Molecular Probes) as a reference. After further incubation for 10 minutes in dark 200 nM α,β-methylene ATP agonist was added to initiate the Ca^{2+} mobilization. Fluorescence intensity was measured by FDSS-6000 (λ_{ex}=410nm, λ_{em}=510nm / Hamamatsu Photonics) at 250 msec intervals. Integral ratios were calculated from the data and compared with that of a control.

[Measurement of capsaicin-induced bladder contraction in anesthetized rats] (Assay 4)

(1) Animals

Female Sprague-Dawley rats (200~250 g / Charles River Japan) were used.

(2) Catheter implantation

Rats were anesthetized by intraperitoneal administration of urethane (Sigma) at 1.2 g/kg. The abdomen was opened through a midline incision, and a polyethylene catheter (BECTON DICKINSON, PE50) was implanted into the bladder through the dome. In parallel, the inguinal region was incised, and a polyethylene catheter (Hibiki, size 5) filled with 2 IU / ml of heparin (Novo Heparin, Aventis Pharma) in saline (Otsuka) was inserted into a common iliac artery.

(3) Cystometric investigation

The bladder catheter was connected via T-tube to a pressure transducer (Viggo-Spectramed Pte Ltd, DT-XXAD) and a microinjection pump (TERUMO). Saline was infused at room temperature into the bladder at a rate of 2.4 ml/hr. Intravesical pressure was recorded continuously on a chart pen recorder (Yokogawa). At least three reproducible micturition cycles, corresponding to a 20-minute period, were recorded before a test compound administration and used as baseline values.

(4) Administration of test compounds and stimulation of bladder with capsaicin

The saline infusion was stopped before administrating compounds. A testing compound dissolved in the mixture of ethanol, Tween 80 (ICN Biomedicals Inc.) and saline (1 : 1 : 8, v/v/v) was administered intraarterially at 10 mg/kg. 2min after the administration of the compound 10 μg of capsaicin (Nacalai Tesque) dissolved in ethanol was administered intraarterially.

(5) Analysis of cystometry parameters

Relative increases in the capsaicin-induced intravesical pressure were analyzed from the cystometry data. The capsaicin-induced bladder pressures were compared with the maximum bladder pressure during micturition without the capsaicin stimulation. The testing compounds–mediated inhibition of the increased bladder pressures was evaluated using Student's t-test. A probability level less than 5% was accepted as significant difference.

Results of IC_{50} of capsaicin-induced Ca^{2+} influx in the human VR1-transfected CHO cell line are shown in Examples and tables of the Examples below. The data corresponds to the compounds as yielded by solid phase synthesis and thus to levels of purity of about 40 to 90%. For practical reasons, the compounds are grouped in four classes of activity as follows:

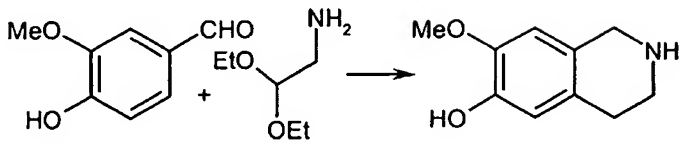
IC_{50} = A 0.1μM < B 0.5 μM < C 1 μM < D

The compounds of the present invention also show excellent selectivity, and strong activity in other assays (2)-(4) described above .

Preparing method of starting compounds:

[Starting compound A]

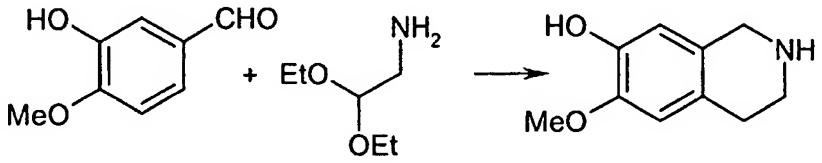
7-methoxy-1, 2,3,4-tetrahydro-6-isoquinolinol



An ethanol (15 ml) solution of aminoacetaldehyde diethyl acetal (2.66 g, 20.0 mmol) and vanillin (3.04 g, 20.0 mmol) was added to a suspension of platinum (prepared by reduction of 0.2 g of platinum oxide) in ethanol (20 ml). The mixture was stirred under a hydrogen atmosphere at room temperature for 4 hrs. The catalyst was removed and the solvent was evaporated under reduced pressure. The residue was dissolved in 6N HCl (150 ml) and Pd/C (2.0g, 10%) was added. The reaction mixture was stirred under a hydrogen atmosphere at room temperature for 16 hrs. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was collected and washed with ethanol to give 7-methoxy-1, 2,3,4-tetrahydro-6-isoquinolinol (0/75 g, 25%).

[Starting compound B]

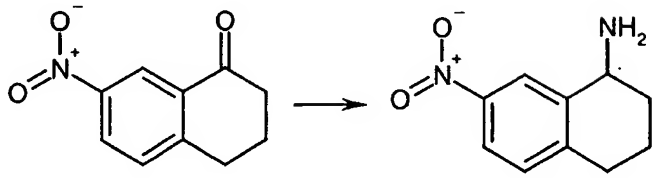
6-methoxy-1, 2,3,4-tetrahydro-7-isoquinolinol



Starting material B was prepared by the same method as for starting material A, using isovanillin instead of vanillin. 6-methoxy-1,2,3,4-tetrahydro-7-isoquinolinol (0.03g, 35%).

[Starting compound C]

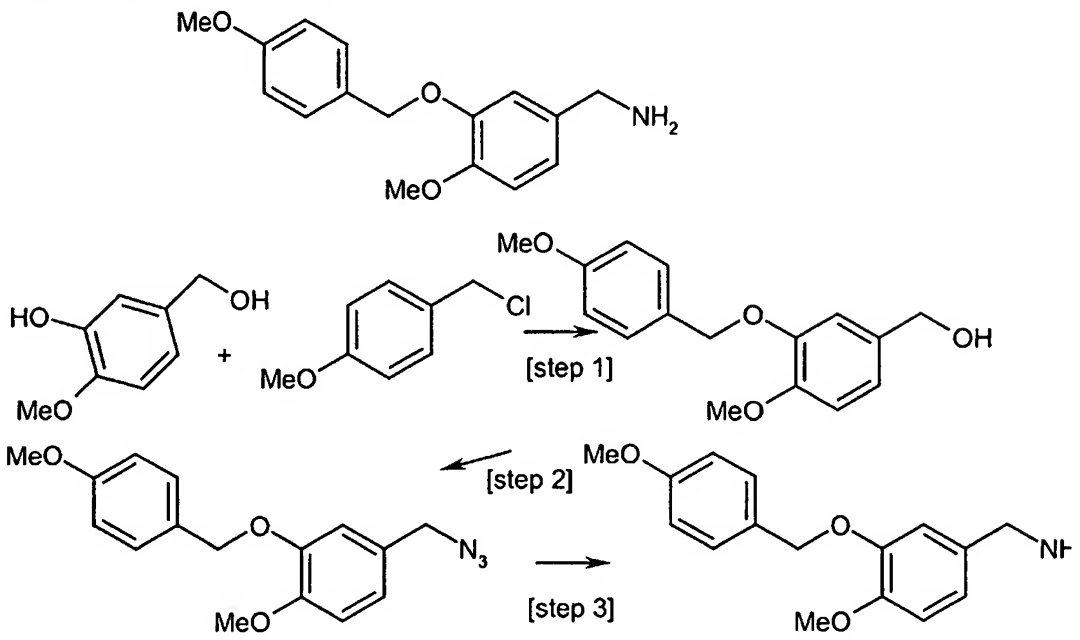
7-nitro-1, 2,3,4-tetrahydro-1-naphthalenamine



A mixture of 7-nitro-1-tetralone (1.91 g, 10.0 mmol), titanium (IV)tetraisopropoxide (5.9 ml, 20.0 mmol), ammonium chloride (1.07 g, 20.0 mmol) and triethylamine (2.8 ml, 20.0 mmol) in ethanol (20 ml) was stirred for 16 hrs at room temperature. Sodium tetrahydroborate (0.57 g, 15.0 mmol) was added and the reaction mixture was stirred for another 7 hrs at room temperature. 2M aqueous ammonia (30 ml) was added and after filtration of the inorganic precipitate, extraction was carried out with diethylether. The organic layer was then extracted with 2M HCl. The HCl solution was washed with diethylether and then treated with 2M NaOH. Extraction with diethylether was carried out. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated to give 7-nitro-1,2,3,4-tetrahydro-1-naphthalenamine (0.25 g, 20%)

[Starting compound D]

4-(aminomethyl)-1-methoxy-2-[(4-methoxybenzyl) oxy]benzene



Step 1: To a suspension of 3-hydroxy-4-methoxybenzyl alcohol (2.00 g, 13.0 mmol) and K_2CO_3 (2.13 g, 13.6 mmol) in acetone (80 ml) was added methoxybenzylchloride (2.13 g, 13.6 mmol). The reaction mixture was stirred at 60 °C for 16 hrs. The mixture was concentrated under reduced pressure and the residue was dissolved in AcOEt/water. Extraction was carried out with AcOEt and the organic layer was washed with brine, dried over Na_2SO_4 and then concentrated under reduced pressure to give {4-methoxy-3-[(4-methoxybenzyl)oxy]phenyl}methanol (quantitative yield).

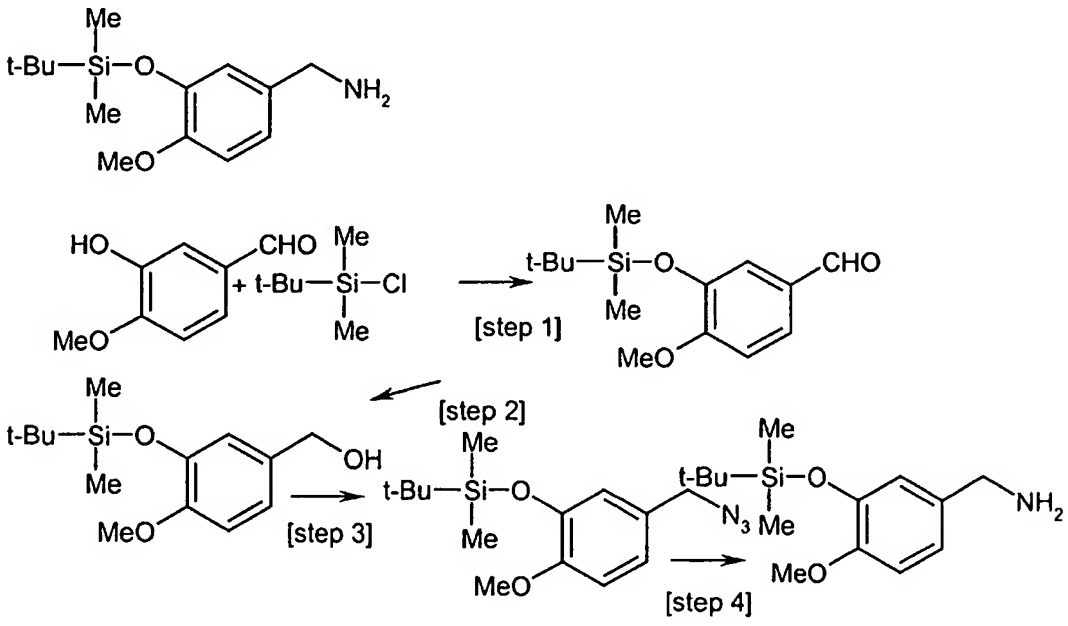
Step 2: To a mixture of {4-methoxy-3-[(4-methoxybenzyl)oxy]phenyl}methanol (1.00 g, 3.7 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.61 g, 4.0 mmol) in toluene (18 ml) was added diphenylphosphinyl azide (1.10 g, 4.0 mmol) at 0°C. The mixture was stirred at room temperature for 4 hrs. Water was added and extraction was carried out with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was passed through a silica gel plug

(hexane:AcOEt = 1:1) and the filtrate was concentrated under reduced pressure to give 4-(azidomethyl)-1-methoxy-2-[(4-methoxybenzyl)oxy]benzene (1.00 g, 92%)which was used for the next step without any further purification.

Step 3: To a solution of 4-(azidomethyl)-1-methoxy-2-[(4-methoxybenzyl)oxy]benzene (1.00 g, 3.3 mmol) in THF (33 ml) was added triphenylphosphine (2.63 g, 10.0 mmol) and water (0.25 ml) at room temperature. The reaction mixture was stirred at room temperature for 16 hrs and then concentrated under reduced pressure. The residue 4-(aminomethyl)-1-methoxy-2-[(4-methoxybenzyl)oxy]benzene was used in the reaction with isocyanates following method A without any further purification.

[Starting compound E]

(3-{[tert-butyl(dimethyl)silyl]oxy}-4-methoxyphenyl)methanamine



Step 1: To a solution of 3-hydroxy-4-methoxybenzaldehyde (3.00 g, 19.7 mmol) and imidazole (1.61 g, 23.7 mmol) in DMF (40 ml) was added t-butyldimethylsilylchloride (3.12 g, 20.7 mmol) at 0°C. The reaction mixture was

stirred at room temperature for 4 hrs and then diluted with diethylether. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated under reduced pressure. The residue product was used in the next step without any further purification.

Step 2: To a solution of 3-{[tert-butyl(dimethyl)silyl]oxy}-4-methoxybenzaldehyde (5.25 g, 19.7 mmol) was added $NaBH_4$ (0.75 g, 19.7 mmol) and the reaction mixture was stirred at room temperature for 16 hrs. Saturated NH_4Cl solution was added and the solvent was removed under reduced pressure. The residue was extracted with AcOEt and the organic layer was washed with brine and dried over Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Hexane:AcOEt = 9:1 – 3:1) to give (3-{[tert-butyl(dimethyl)silyl]oxy}-4-methoxyphenyl)methanol (4.51 g, 85%).

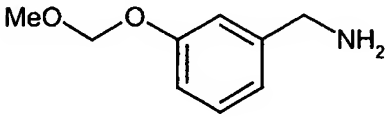
Step 3: To a mixture of (3-{[tert-butyl(dimethyl)silyl]oxy}-4-methoxyphenyl)methanol (1.00 g, 3.7 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.60 g, 3.9 mmol) in toluene (18 ml) was added diphenylphosphinyl azide (1.08 g, 3.9 mmol) at 0°C. The mixture was stirred at room temperature for 4 hrs. Water was added and extraction was carried out with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was passed through a silica gel plug (hexane:AcOEt = 1:1) and the filtrate was concentrated under reduced pressure to give [5-(azidomethyl)-2-methoxyphenoxy](tert-butyl)dimethylsilane (1.09 g, quantitative) which was used for the next step without any further purification.

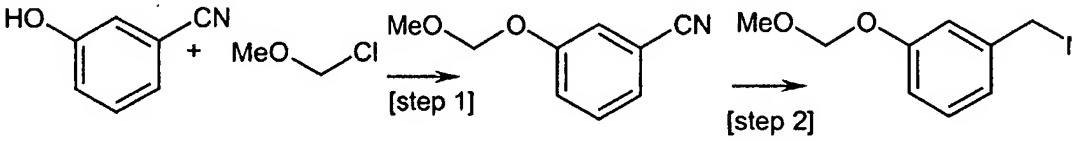
Step 4: To a solution of [5-(azidomethyl)-2-methoxyphenoxy](tert-butyl) dimethylsilane (1.09 g, 3.7 mmol) in AcOEt (20 ml) was added 10% Pd/C (0.10 g) and the reaction mixture was stirred at room temperature for one day under a hydrogen atmosphere. The catalyst was removed by filtration and the

filtrate was concentrated under reduced pressure. The residue was washed with diisopropyl ether and hexane to give (3-{[tert-butyl(dimethyl)silyl]oxy}-4-methoxyphenyl)methanamine which was used in the next step without any further purification.

[Starting compound F]

[3-(methoxymethoxy)phenyl]methanamine



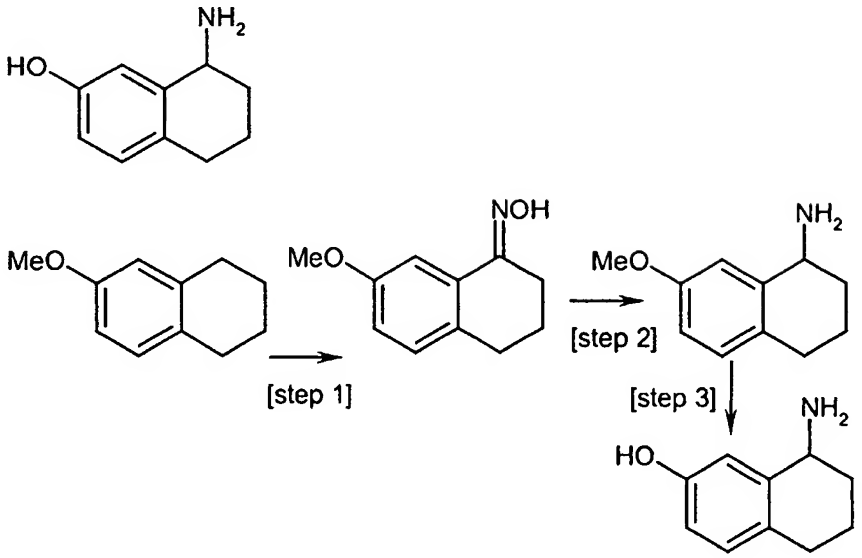


Step 1: To a solution of 3-hydroxybenzonitrile (5.00 g, 42.0 mmol) and N,N-diisopropylethylamine (8.14 g, 63.0 mmol) in CH_2Cl_2 (100 ml) was added chlorodimethyl ether (4.06 g, 50.4 mmol) at 0°C. The reaction temperature was allowed to rise to room temperature over 30 minutes. The mixture was then stirred at room temperature for 3 hrs. The mixture was then washed with water, dried over Na_2SO_4 and then concentrated under reduced pressure. 3-(methoxymethoxy)benzonitrile (4.24 g, 62%) was obtained as clear oil.

Step 2: To a cooled (0°C) suspension of lithiumaluminiumhydride (0.84 g, 22.1 mmol) in THF (50 ml) was added dropwise a solution of 3-(methoxymethoxy) benzonitrile (3.00 g, 18.4 mmol) in THF (10 ml). The reaction mixture was stirred at 0°C for 1 hr and then at room temperature for 3 hrs. A 5 N NaOH solution was added dropwise at 0°C and the resulting precipitate was filtered off. The filtrate was concentrated under reduced pressure and the residue was dissolved in AcOEt. This was washed with water, dried over Na_2SO_4, and then concentrated under reduced pressure to give [3-(methoxymethoxy)phenyl]methanamine (1.78 g, 58%).

[Starting compound G]

8-amino-5,6,7,8-tetrahydro-2-naphthalenol



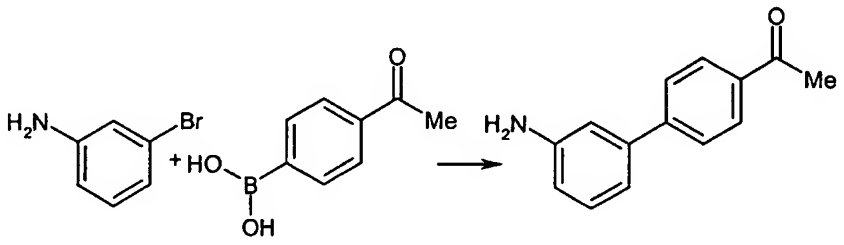
Step 1: A mixture of 7-methoxy-1-tetraline (5.00 g, 28.4 mmol), hydroxylamine hydrochloride (5.92 g, 85.1 mmol) and potassium carbonate 12.94 g, 93.6 mmol) in methanol (100 ml) was heated to reflux and stirred for 16 hrs. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. Water was added to the residue and extraction was carried out with AcOEt. The organic layer was dried over Na_2SO_4 and then concentrated to give 7-methoxy-3,4-dihydro-1(2H)-naphthalenone oxime (5.51 g, quantitative).

Step 2: To a suspension of Pd/C (10%) in methanol (10 ml) was added a catalytic amount of acetic acid and 7-methoxy-3,4-dihydro-1(2H)-naphthalenone oxime (2.00 g, 10.5 mmol). The mixture was stirred under a hydrogen atmosphere at room temperature for 16 hrs. The Pd catalyst was removed and the filtrate was concentrated under reduced pressure. Water was added to the residue and extraction was carried out with AcOEt. The organic layer was dried over Na_2SO_4 and then concentrated to give of 7-methoxy-1,2,3,4-tetrahydro-1-naphthalenamine (2.00 g, quantitative).

Step 3: To a solution of 7-methoxy-1,2,3,4-tetrahydro-1-naphthalenamine (0.20 g,1.1 mmol) in CH_2Cl_2 (5 ml) was added boron tribromide (1.5 ml, 1M solution in CH_2Cl_2) at 0°C. Water was then added to the reaction mixture and extraction was carried out with AcOEt. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure to give 8-amino-5,6,7,8-tetrahydro-2-naphthalenol (0.18 g, 98%)

[Starting compound H]

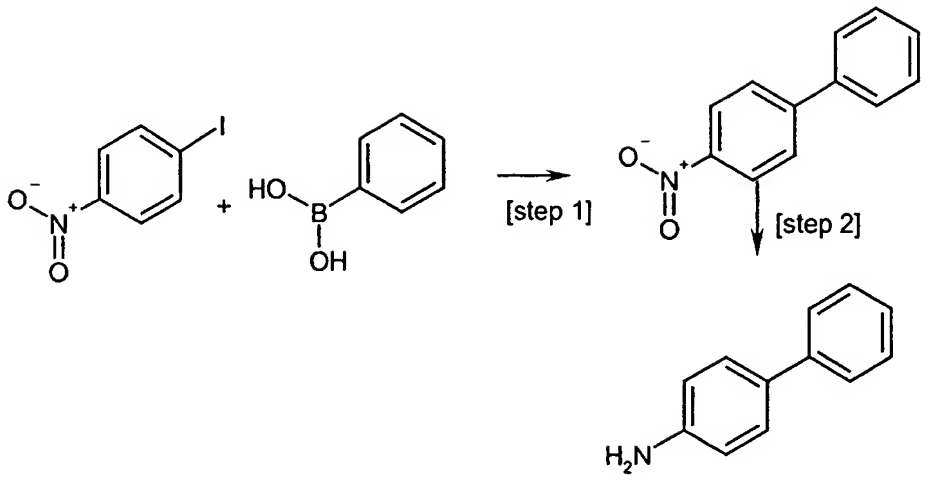
1-(3'-amino-1,1'-biphenyl-4-yl)ethanone



To a stirred solution of 3-bromoaniline (0.344 g, 2.00 mmol) and $[Pd(PPh_3)_4]$ (0.069 g, 0.06 mmol) in DMF was added a 2N solution of sodium carbonate (1.5 ml). 4-acetylphenylboronic acid (0.656 g, 4.00 mmol) was added and the mixture was stirred at 90 °C for 16 hrs. The reaction mixture was then washed with water and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the resulting residue was purified by preparative thin layer chromatography on silica gel ($CHCl_3$) to give 1-(3'-amino-1,1'-biphenyl-4-yl)ethanone (0.25 g, 60 %).

[Starting compound I]

4-amino-1,1'-biphenyl

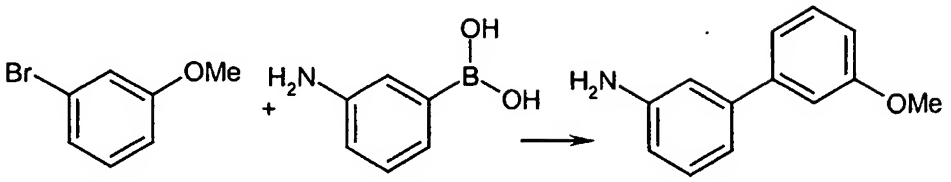


Step 1: To a stirred mixture of $[Pd(PPh_3)_4]$ (0.069 g, 0.06 mmol), K_3PO_4 (0.636 g, 3.00 mmol) and 4-iodonitrobenzene (0.498 g, 2.00 mmol) in DMF was added phenylboronic acid (0.243 g, 2.00 mmol) and the mixture was stirred at 100 °C for 6 hrs. The reaction mixture was then washed with water and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (5% AcOEt-Hexane) to give 4-nitro-1,1'-biphenyl (0.28 g, 69%).

Step 2: To a solution of 4-nitro-1,1'-biphenyl (0.275 g, 1.40 mmol) in ethanol (30 ml) was added Pd/C (0.050 g, 10% with 51.5% water) and the mixture was stirred at room temperature under a hydrogen atmosphere for 5 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give 4-amino-1,1'-biphenyl (0.21g, 88%)

[Starting compound J]

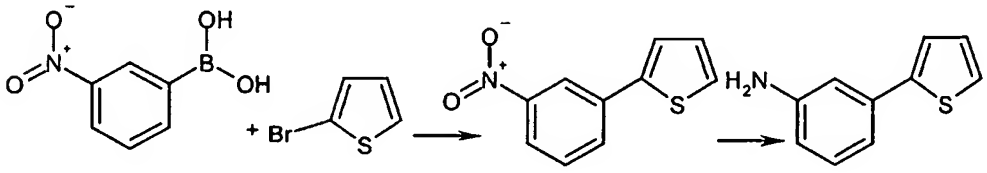
3'-methoxy-1,1'-biphenyl-3-amine



To a stirred solution of 3-bromoanisole (0.374 g, 2.00 mmol) and $[Pd(PPh_3)_4]$ (0.069 g, 0.06 mmol) in DMF was added a 2N solution of sodium carbonate (1.5 ml). 3-aminophenylboronic acid (0.548 g, 4.00 mmol) was added and the mixture was stirred at 90 °C for 16 hrs. The reaction mixture was then washed with water and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the resulting residue was purified by preparative thin layer chromatography on silica gel ($CHCl_3$, IPE:Hexane = 1:1) to give 3'-methoxy-1,1'-biphenyl-3-amine (0.28 g, 92 %).

[Starting compound K]

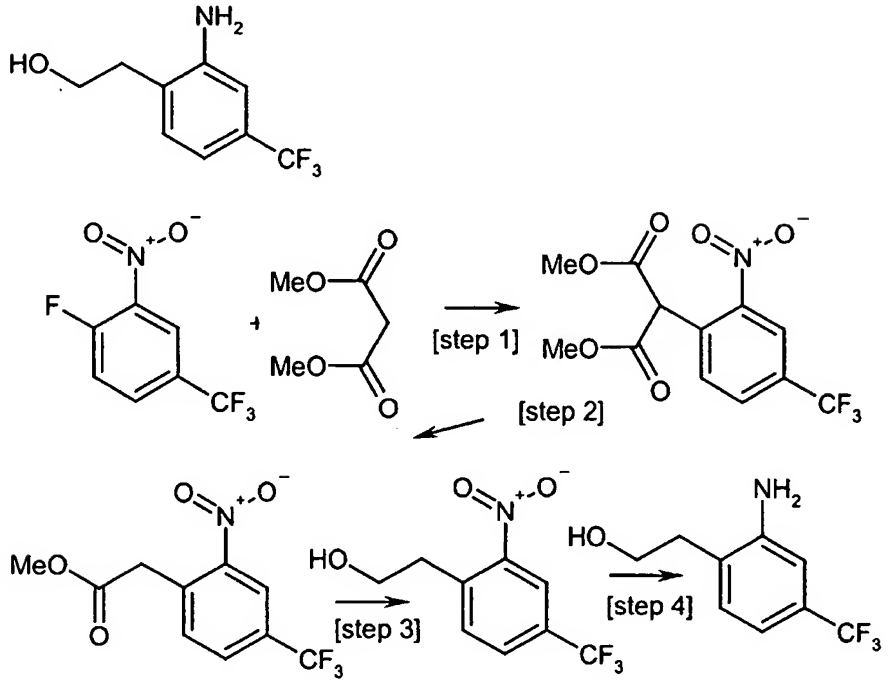
3-(2-thienyl)aniline



To a stirred mixture of $[Pd(PPh_3)_4]$ (0.069 g, 0.06 mmol), K_3PO_4 (0.636 g, 3.00 mmol) and 2-bromothiophene (0.343 g, 2.00 mmol) in DMF was added 3-nitrophenylboronic acid (0.335 g, 2.00 mmol) and the mixture was stirred at 100 °C for 6 hrs. The reaction mixture was then washed with water and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the resulting residue was dissolved in ethanol (30 ml). Pd/C (0.050 g, 10% with 51.5% water) was added and the reaction mixture was stirred at room temperature under a hydrogen atmosphere for 5 hrs. The reaction mixture was filtered and the filtrate was concentrated to give 3-(2-thienyl)aniline (0.35 g, 86 %).

[Starting compound L]

2-[2-amino-4-(trifluoromethyl)phenyl]ethanol



Step 1: To a suspension of 60% sodium hydride in THF/DMF (30 ml, 1:1) was added dimethyl malonate(2.000 g, 9.57 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for another 30 minutes. 4-fluoro-3-nitro benzotrifluoride was added and the reaction mixture was stirred for 16 hrs at room temperature. A saturated NH_4Cl solution was added the mixture was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. The solution was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (hexane:AcOEt = 7:1-3:1) to give dimethyl 2-[2-nitro-4-(trifluoromethyl)phenyl]malonate (1.784 g, 58%).

Step 2: A mixture of 2-[2-nitro-4-(trifluoromethyl)phenyl]malonate (1.780 g, 5.55 mmol), LiCl (0.47 g, 11.11 mmol) in DMSO/water (DMSO 10 ml,

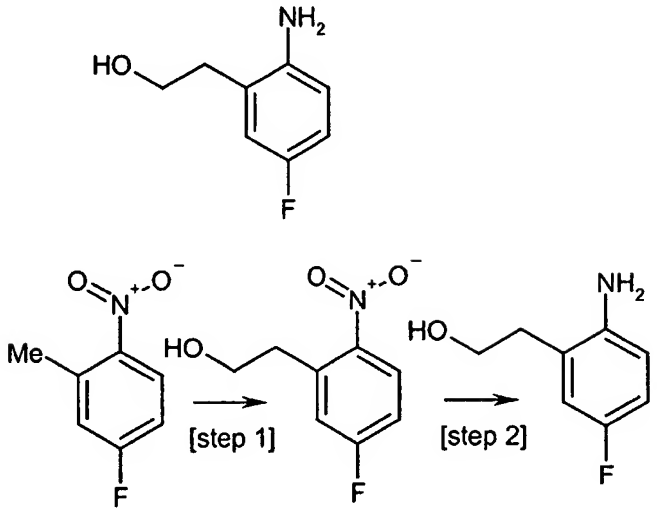
water 0.10 ml) was heated to 100 °C and stirred for 5 hrs. After cooling to room temperature, AcOEt was added and the solution was washed with brine. The organic layer was washed with brine and dried over Na_2SO_4.and then concentrated under reduced pressure. The solution was concentrated under reduced pressure and the resulting residue was triturated with ethyl ether/hexane. Collected to give methyl [2-nitro-4-(trifluoromethyl)phenyl]acetate (0.546 g, 37%).

Step 3: To a solution of methyl [2-nitro-4-(trifluoromethyl)phenyl]acetate (0.546 g, 2.07 mmol) in CH_2Cl_2 (25 ml) was added a 0.9M hexane solution of DIBAH (6.90 ml) at -78°C. The reaction temperature was allowed to rise to 0°C and was stirred for 2 hrs. The reaction was then quenched with iPrOH/H_2O and diluted with AcOEt. SiO_2 was added to the mixture and stirring was continued for another 1 hr. The mixture was passed through a celite pad and the filtrate was concentrated under reduced pressure. The obtained crude residue (0.454 g, 93%) was used in the next step without any further purification.

Step 4: To a solution of 2-[2-nitro-4-(trifluoromethyl)phenyl]ethanol in methanol (20 ml) was added Pd/C (0.050 g, 10%). The solution was stirred at room temperature under a hydrogen atmosphere for 20 hrs. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give 2-[2-amino-4-(trifluoromethyl)phenyl]ethanol. The obtained product was used as starting material without any further purification.

[Starting compound M]

2-(5-fluoro-2-aminophenyl)ethanol



Step 1: To a stirred mixture of 5-fluoro-2-nitrotoluene (0.300 g, 1.93 mmol) and paraformaldehyde (0.023 g, 0.77 mmol) in DMSO (3.0 ml) was added sodium phenoxide trihydrate (0.010 g, 0.06 mmol). The reacting mixture was heated to 60°C and stirred for 1 hr. The resulting mixture was diluted with AcOEt and washed with dil. HCl, water and then brine. The organic layer was dried over Na_2SO_4. The solution was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (hexane:AcOEt = 3:1) to give 2-(5-fluoro-2-nitrophenyl)ethanol.

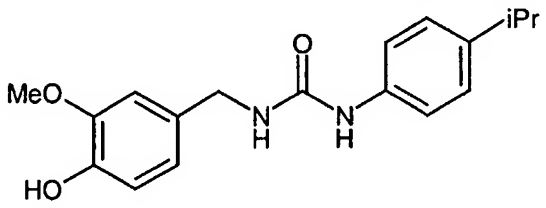
Step 2: A mixture of 2-(5-fluoro-2-nitrophenyl)ethanol (0.123 g, 0.664 mmol), Fe powder (0.300 g, 5.37 mmol) and NH_4Cl (0.100 g, 1.86 mmol) in EtOH/Water (EtOH 8 ml, water 0.4 ml) was stirred at 90°C for 1 hr. After cooling to room temperature, AcOEt was added and the mixture was filtered through a celite pad. The filtrate was concentrated and the residue was dissolved in AcOEt, washed with water and then brine and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography

(hexane:AcOEt = 1:2) to give 2-(5-fluoro-2-aminophenyl)ethanol. (0.09 g, 87%)

Other starting materials are commercially available or can be prepared according to methods reported in the literature.

Example 1-1;

N-(4-hydroxy-3-methoxybenzyl)-N'-(4-isopropylphenyl)urea



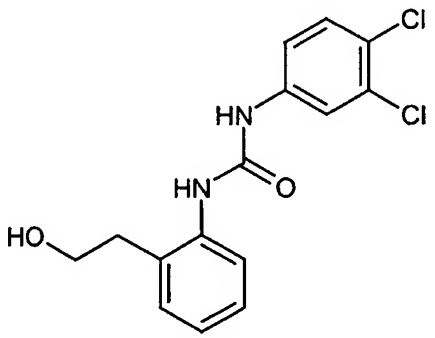
This example was performed according to said method A.

To a stirred solution of 4-(aminomethyl)-2-methoxyphenol hydrochloride (50.0 mg, 0.26 mmol) and triethylamine (26.68 mg, 0.26 mmol) in 1,4-dioxane (1.5 ml) was added a solution of 4-isopropylphenyl isocyanate (38.3 mg, 0.24 mmol) in 1,4-dioxane (1.4 mL) at room temperature. The reaction mixture was warmed to 50 °C, and stirred for 20 hrs at the same temperature. The solvent was removed under reduced pressure, and the residue was purified by preparative thin layer chromatography (MeOH:CHCl3 = 1:20) to give N-(4-hydroxy-3-methoxybenzyl)-N'-(4-isopropylphenyl)urea (21 mg, 25%).

mp 156 °C;
Molecular weight 314.39
Activity grade:A

Example 1-2;

N-(3,4-dichlorophenyl)-N'-[2-(2-hydroxyethyl)phenyl]urea



This example was performed according to the general method A.

A solution of 2-(2-aminophenyl)ethanol (30.0 mg, 0.22 mmol) and 3,4-dichlorophenylisocyanate (41.1 mg, 0.22 mmol) in 1,4-dioxane (2.0 mL) was stirred at 50 °C for 18 hrs. The reaction mixture was cooled to room temperature and diluted with diisopropylether. The precipitate was collected and then washed with $^{i}Pr_2O$ to give N-(3,4-dichlorophenyl)-N'-[2-(2-hydroxyethyl)phenyl]urea (48.9 mg, 69%).

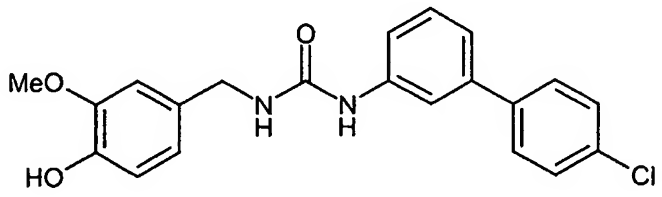
mp 188-190 °C;

Molecular weight 325.20

Activity grade:A

Example 2-1;

N-(4'-chloro-1,1'-biphenyl-3-yl)-N'-(4-hydroxy-3 methoxybenzyl)urea



This example was performed according to said method B.

A mixture of 4-(aminomethyl)-2-methoxyphenol hydrochloride (50.0 mg, 0.26 mmol) and phenyl 4'-chloro-1,1'-biphenyl-3-ylcarbamate (85.4 mg, 0.26 mmol) in DMSO (0.5 ml) was heated to 90°C and stirred for 16 hrs. Water was then added and extraction was carried out with AcOEt. The organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt:hexane = 2:3) to give N-(4'-chloro-1,1'-biphenyl-3-yl)-N'-(4-hydroxy-3 methoxybenzyl)urea (65.0 mg, 64%)

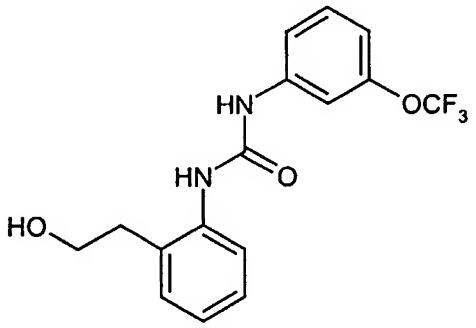
m.p. 153.4°C

Molecular weight 382.85

Activity grade:A

Example 2-2;

N-[2-(2-hydroxyethyl)phenyl]-N'-[3(trifluoromethoxy)phenyl]urea



This example was performed according to the general method B.

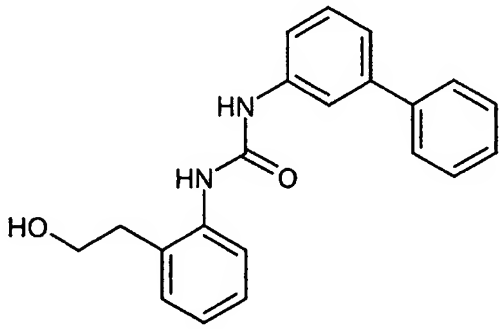
A solution of 2-(2-aminophenyl)ethanol (80.1 mg, 0.58 mmol) and phenyl 3-(trifluoromethoxy)phenylcarbamate (165.3 mg, 0.56 mmol) in DMSO (2.0 mL) was stirred at 90 °C for 1 hr. The reaction mixture was cooled to room temperature and diluted with AcOEt. The solution was washed with 1N HCl, 1N NaOH and brine dried over Na_2SO_4. The solution was then concentrated under reduced pressure, and

the residue was triturated with diisopropylether to give N-[2-(2-hydroxy-ethyl)phenyl]-N'-[3(trifluoromethoxy)phenyl]urea (70.5 mg, 37%).

mp 160-161 °C;
Molecular weight 340.30
Activity grade:A

Example 3-1;

N-(1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea



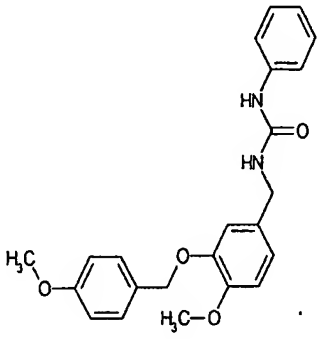
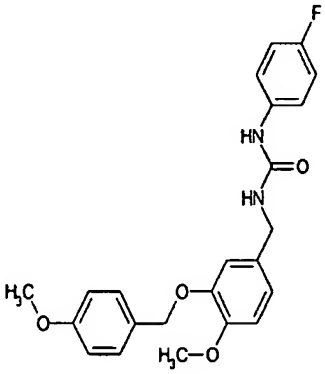
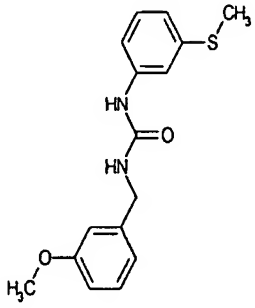
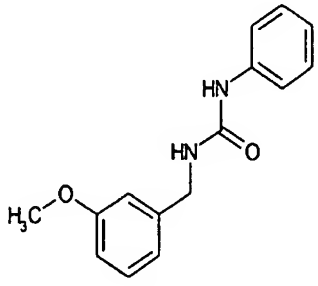
This example was performed according to the general method C.

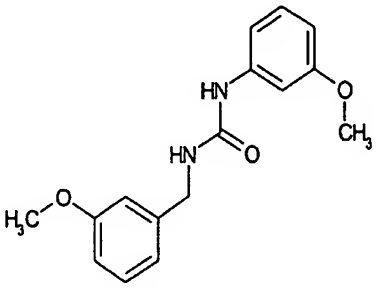
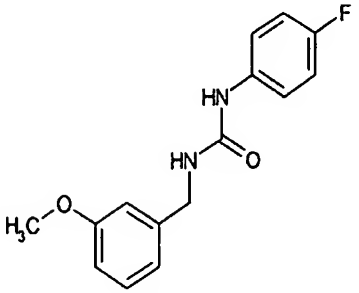
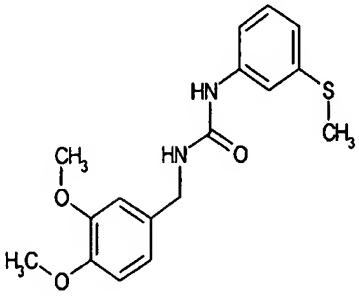
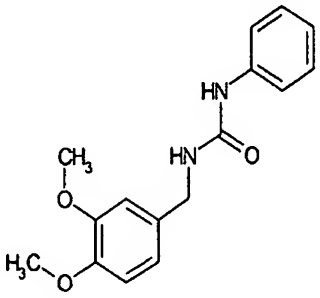
To a solution of 1,1'-biphenyl-3-amine (37.0 mg, 0.22 mmol) in THF (2.0 ml) was added 1'-carbonyldi(1,2,4-triazole) (35.9mg, 0.22 mmol). 2-(2-aminophenyl)ethanol (30.0 mg, 0.22 mmol) was added and the mixture was stirred at 55°C for 18 hrs. After cooling to room temperature, the mixture was diluted with water and ethylalcohol and the resulting precipitate was collected and washed to give N-(1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea (20.8 mg, 29%).

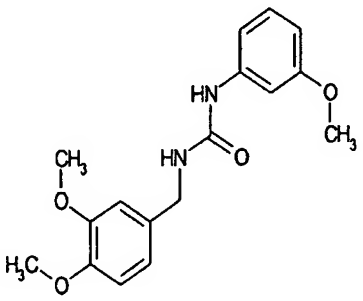
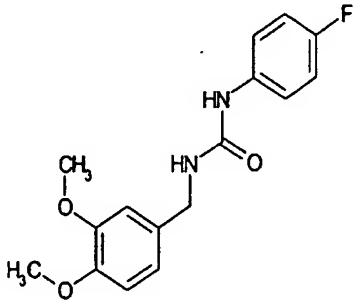
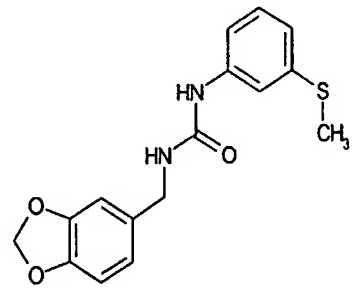
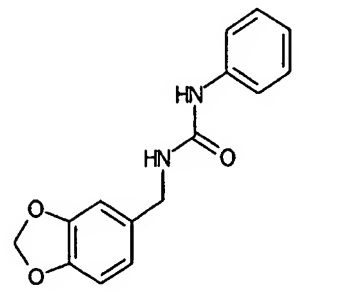
mp 196-198 °C
Molecular weight 332.41
MS (M+H):333
Activity grade:A

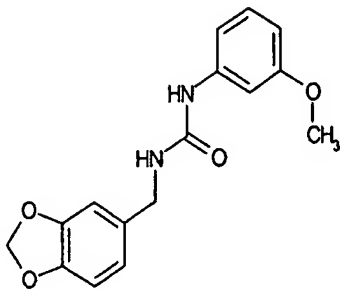
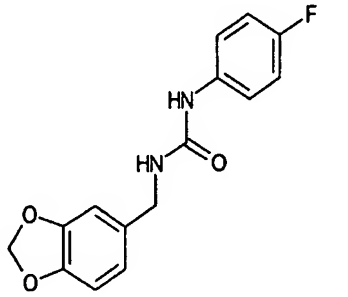
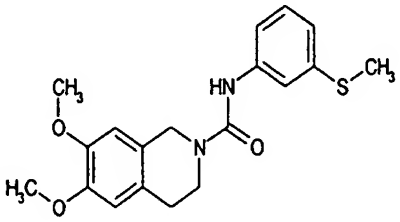
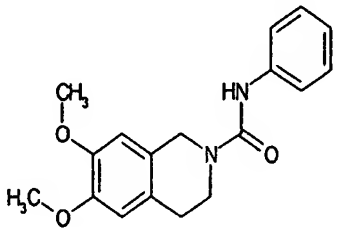
According to procedures similar to any one of the Examples 1 to 3 above, the following compounds were synthesized and tested.

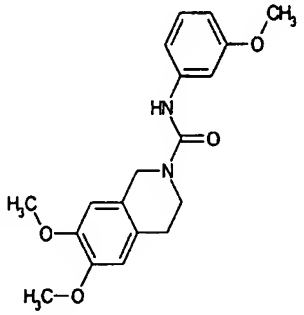
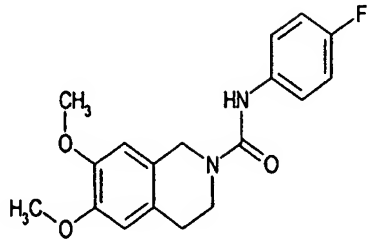
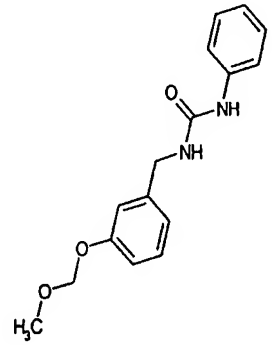
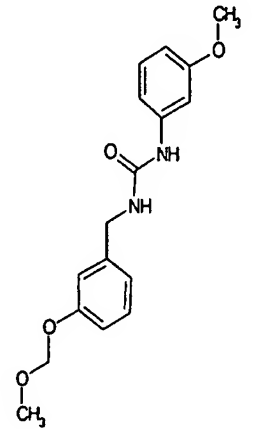
Table 1

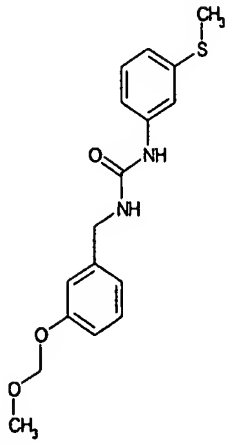
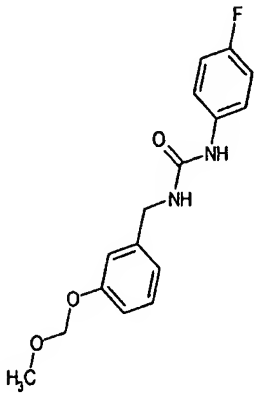
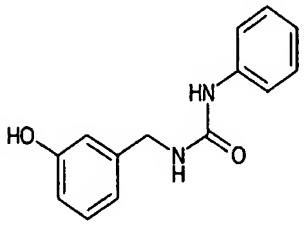
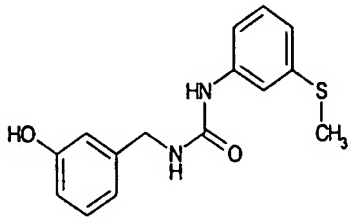
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
6		392,45873	393	ND	C
7		410,44916	411	ND	C
8		302,39806	303	ND	C
9		256,30697	257	ND	C

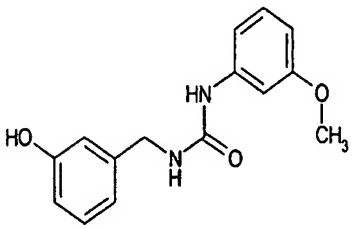
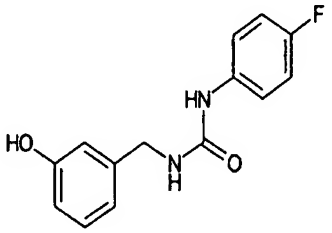
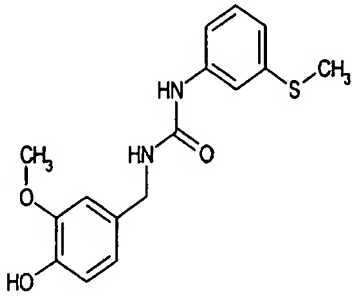
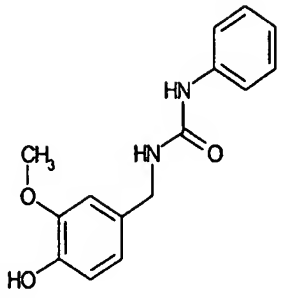
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
10		286,33346	287	ND	C
11		274,2974	275	ND	C
12		332,42455	333	ND	C
13		286,33346	287	ND	C

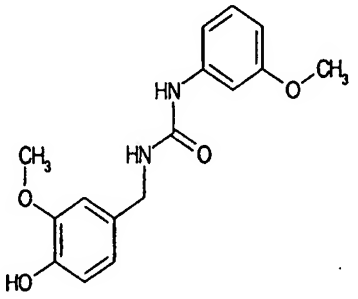
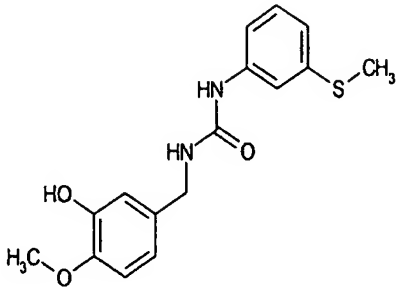
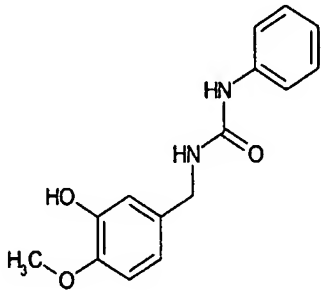
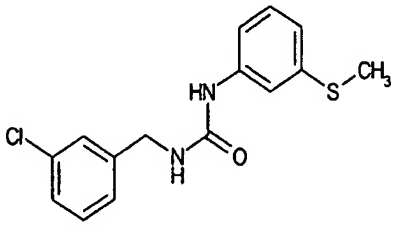
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
14		316,35995	317	ND	C
15		304,32389	305	ND	C
16		316,38152	317	ND	C
17		270,29043	271	ND	C

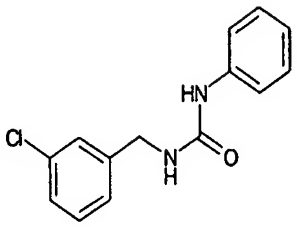
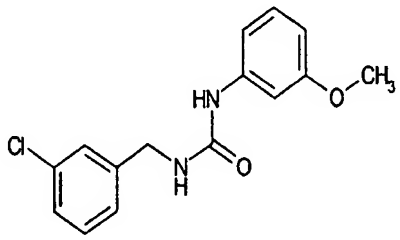
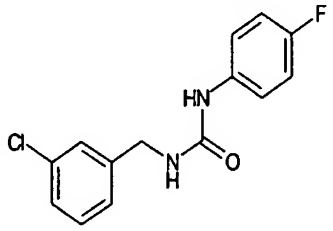
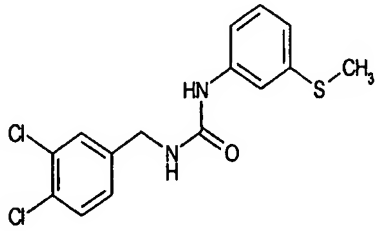
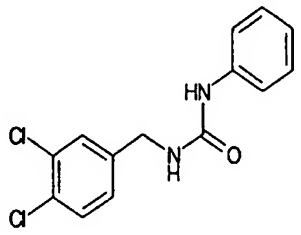
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
18		300,31692	301	ND	C
19		288,28086	289	ND	C
20		358,46279	359	ND	C
21		312,3717	313	ND	C

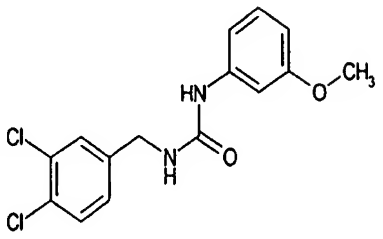
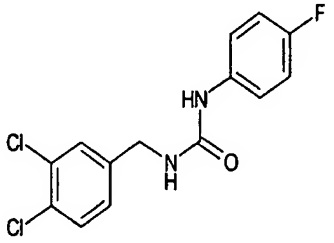
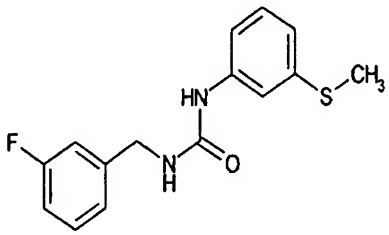
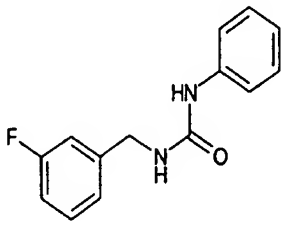
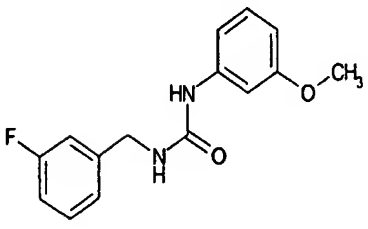
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
22		342,39819	343	ND	C
23		330,36213	331	ND	C
24		286,33346	287	ND	C
25		316,35995	317	ND	C

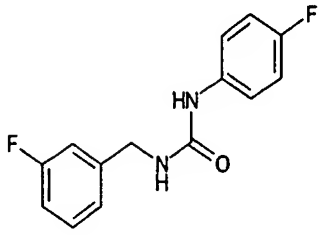
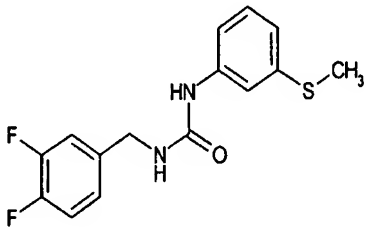
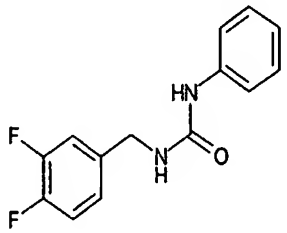
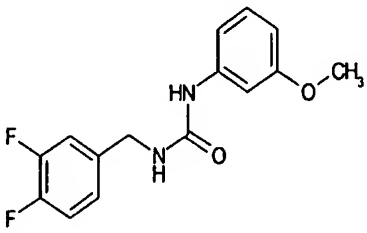
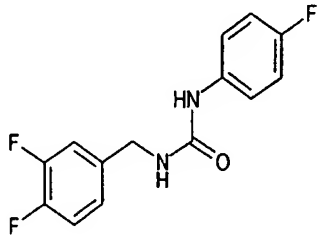
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
26		332,42455	333	ND	C
27		304,32389	305	ND	C
28		242,27988	243	ND	C
29		288,37097	289	ND	C

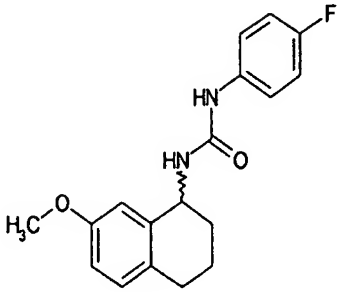
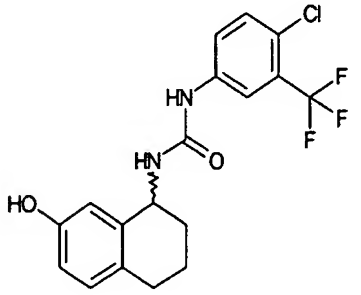
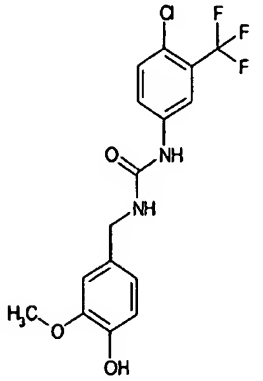
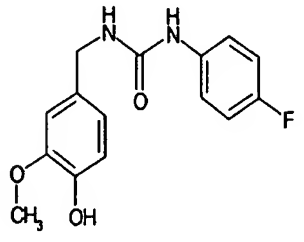
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
30		272,30637	273	ND	C
31		260,27031	261	ND	C
32		318,39746	319	ND	B
33		272,30637	273	ND	C

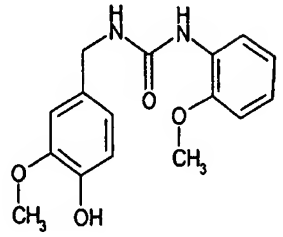
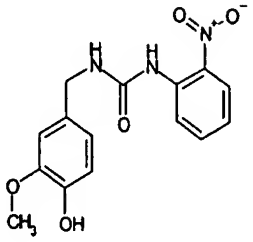
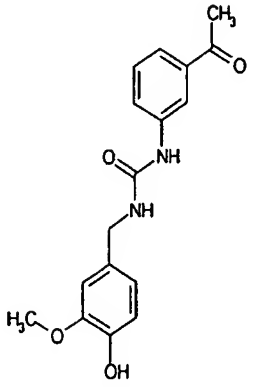
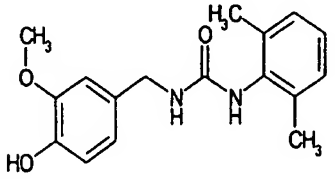
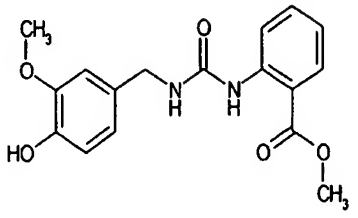
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
34		302,33286	303	133	C
35		318,39746	319	ND	C
36		272,30637	273	ND	C
37		306,8166	307	ND	C

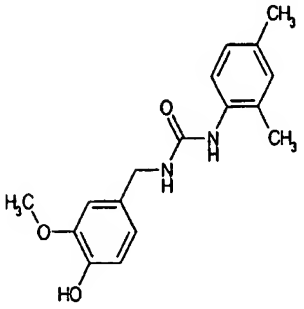
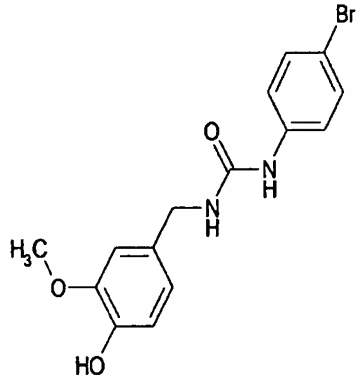
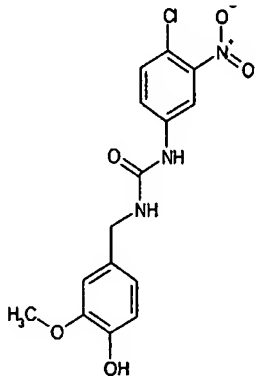
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
38		260,72551	261	ND	C
39		290,752	291	ND	C
40		278,71594	279	ND	C
41		341,26163	341	ND	C
42		295,17054	295	ND	B

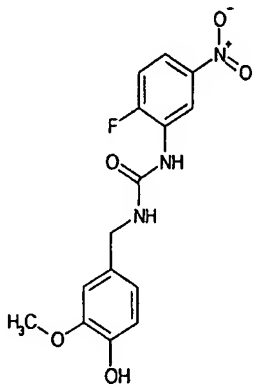
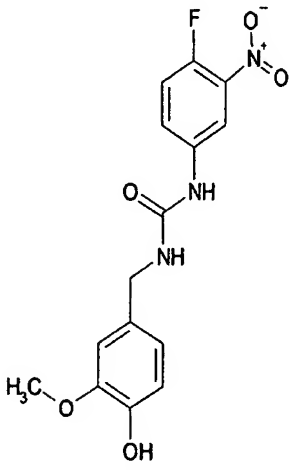
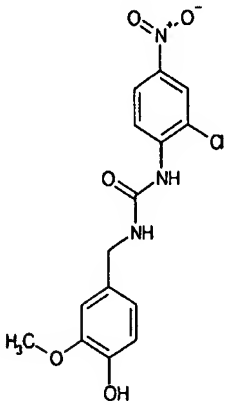
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
43		325,19703	325	ND	B
44		313,16097	313	ND	B
45		290,362	291	ND	C
46		244,27091	245	ND	C
47		274,2974	275	ND	C

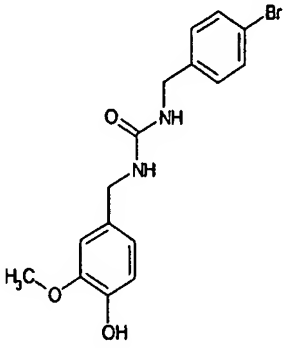
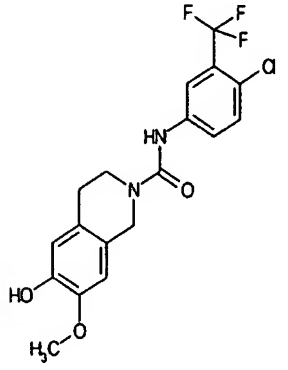
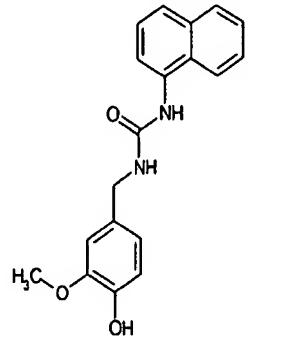
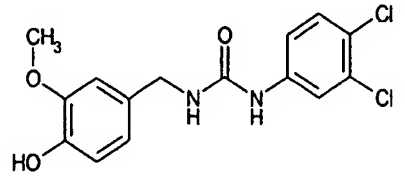
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
48		262,26134	263	ND	C
49		308,35243	309	ND	C
50		262,26134	263	ND	C
51		292,28783	293	ND	C
52		280,25177	281	ND	C

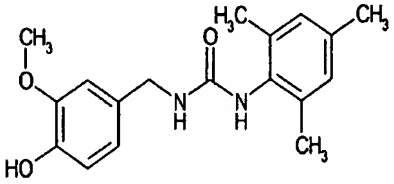
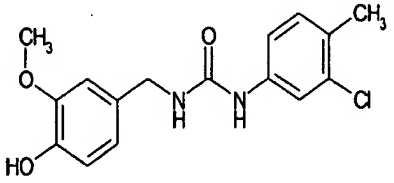
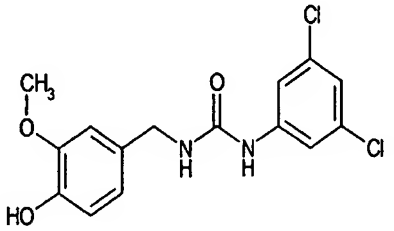
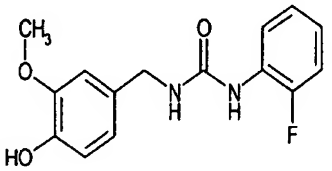
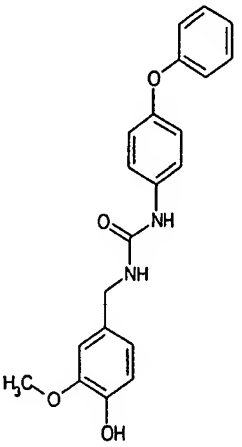
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
53		314,36273		177.5	C
54		384,78862		201	B
55		374,74978		193	A
56		290,2968		211-212	C

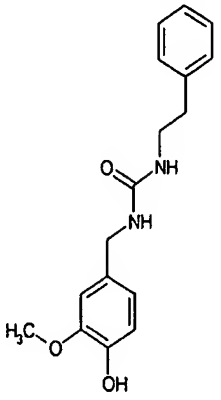
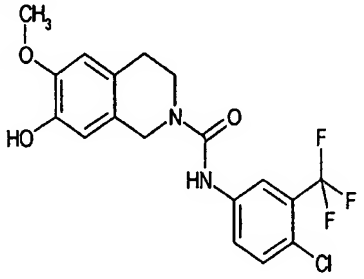
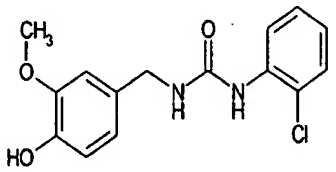
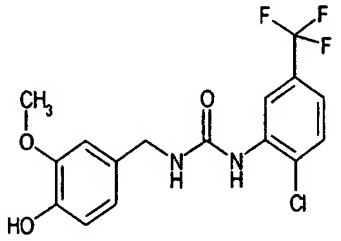
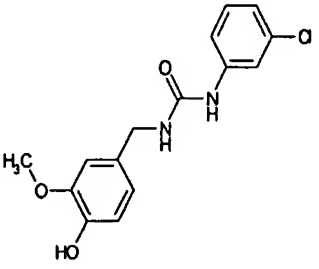
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
57		302,33286		144	C
58		317,3039		180	C
59		314,34401	315	ND	C
60		300,36055		211	C
61		330,34341	331	ND	C

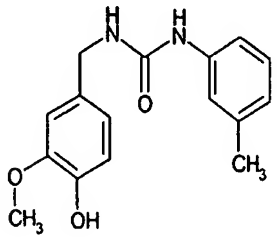
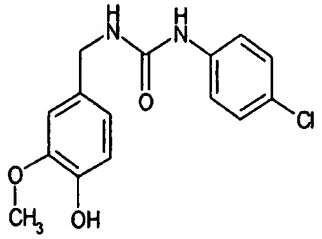
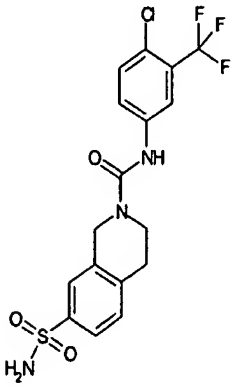
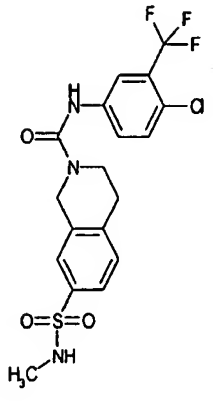
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
62		300,36055		184	C
63		351,2024		203	B
64		351,74893		180	B

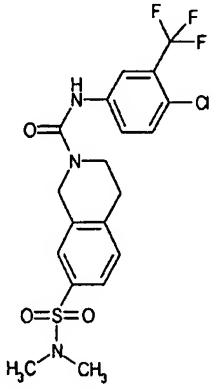
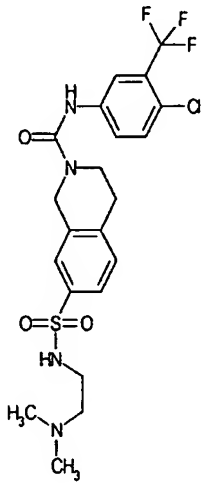
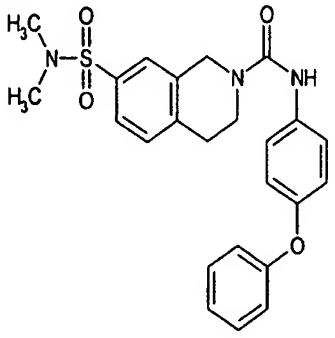
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
65		335,29433		208	C
66		335,29433		184	B
67		351,74893		195Z	C

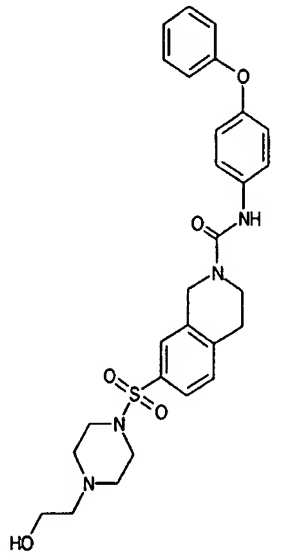
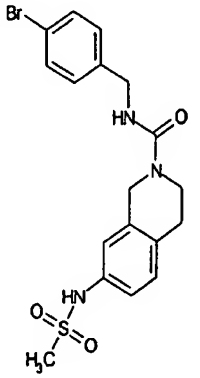
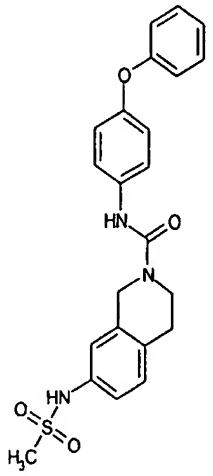
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
68		365,22949		195Z	B
69		400,78802	401	ND	B
70		322,36691		149	A
71		341,19643		207	A

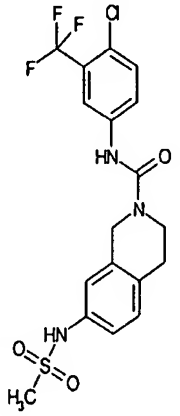
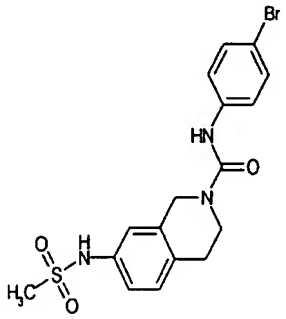
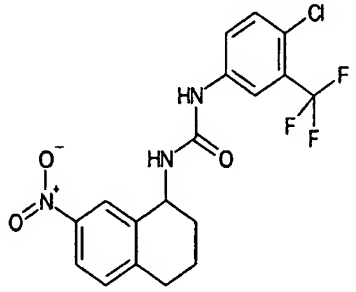
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
72		314,38764		217	C
73		320,77849	321	ND	A
74		341,19643	342	ND	?
75		290,2968	291	ND	B
76		364,40455	364	ND	A

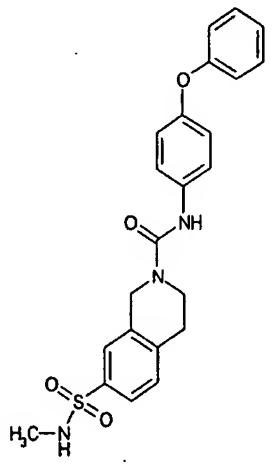
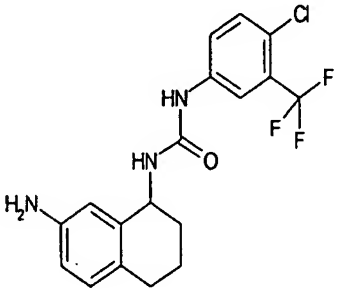
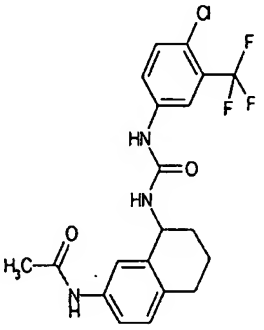
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
77		300,36055	301	ND	B
78		400,78802		130	B
79		306,7514	306	ND	B
80		374,74978	375	ND	A
81		306,7514	307	ND	A

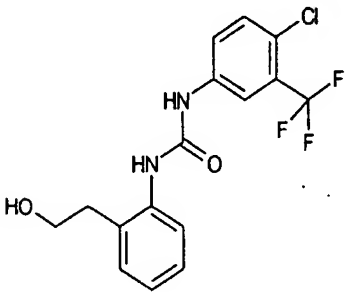
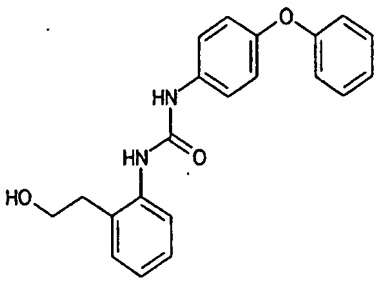
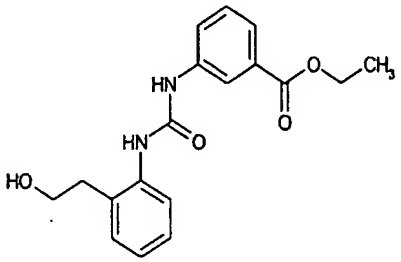
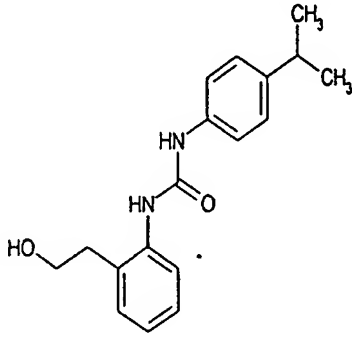
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
82		286,33346		181	B
83		306,7514		210	A
84		433,8396	ND	ND	B
85		447,86669	448	ND	C

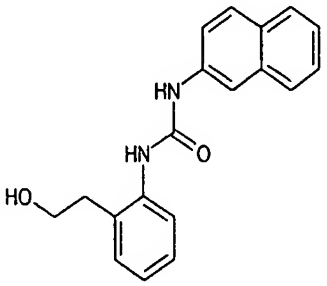
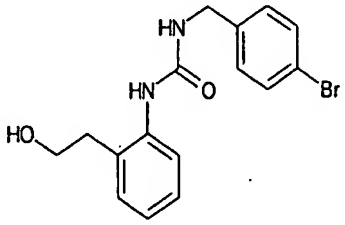
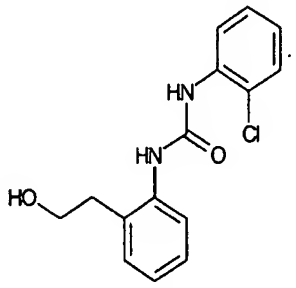
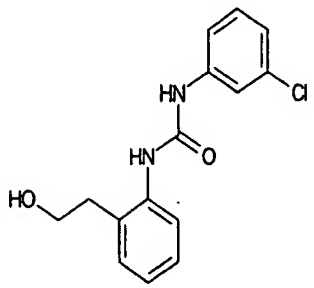
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
86		461,89378	ND	ND	C
87		504,96263	505	ND	C
88		451,54855	452	ND	C

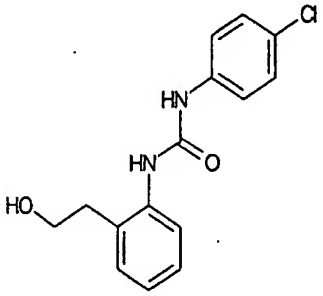
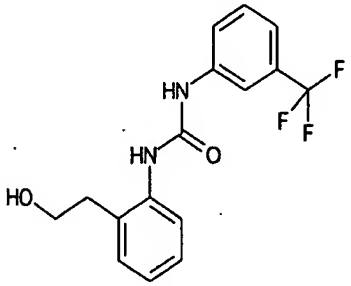
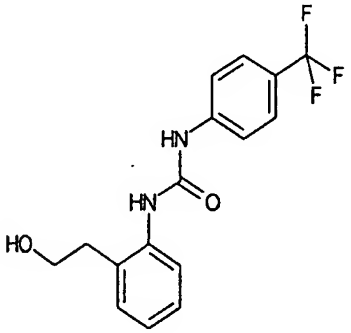
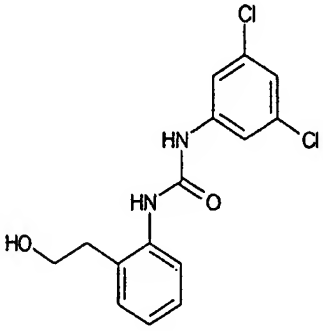
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
89		536,65504	537	ND	C
90		438,3464	439	ND	C
91		437,52146	438	ND	C

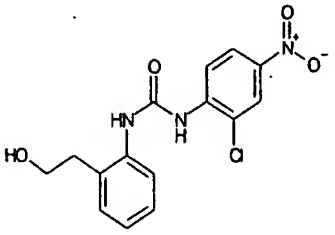
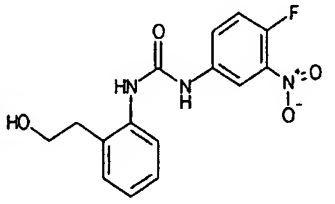
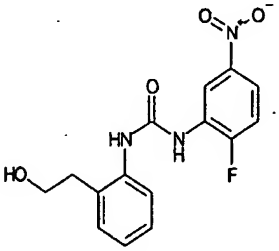
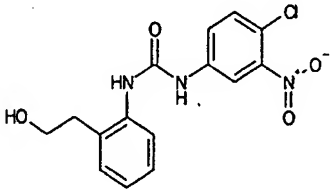
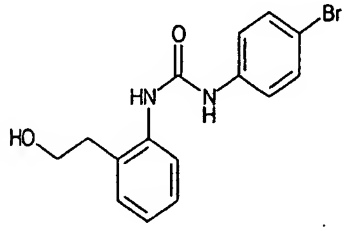
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
92		447,86669	448	ND	B
93		424,31931	425	ND	C
94		413,78675	414	ND	C

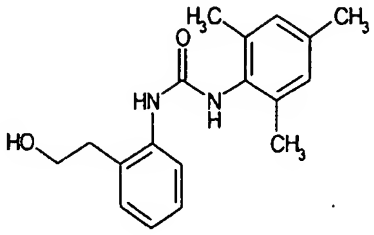
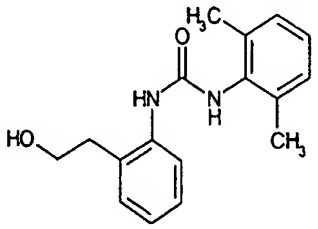
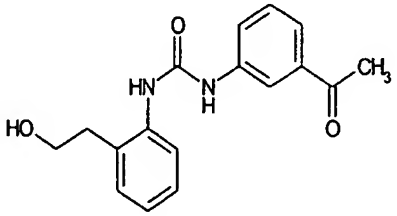
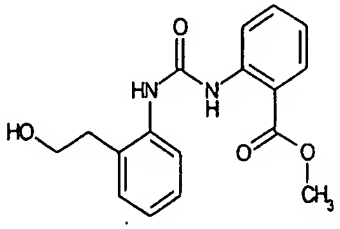
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
95		437,52146	ND	ND	C
96		383,80389		178	C
97		425,84153	426	ND	C

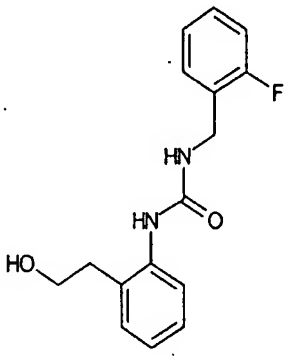
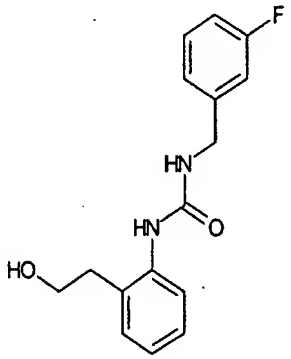
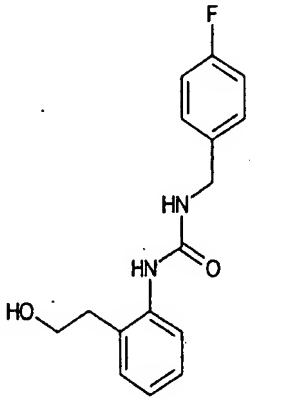
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
98		358,75038		175-177	A
99		348,40515		133-135	A
100		328,3711		152-153	B
101		298,38824		149-150	B

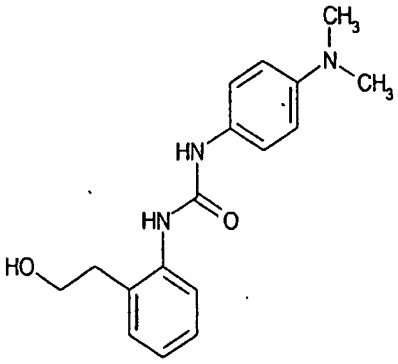
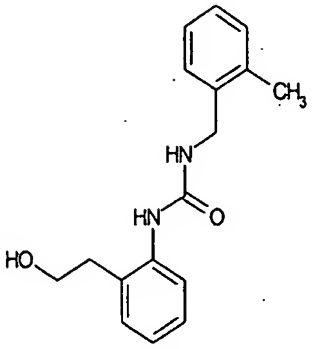
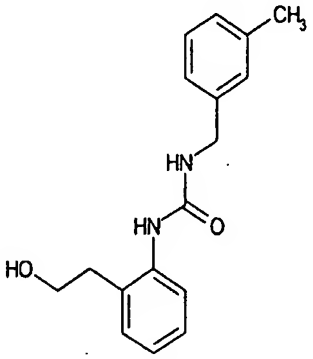
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
102		306,36751		195-197	B
103		349,23009		198-200	B
104		290,752		173-175	C
105		290,752		188-190	C

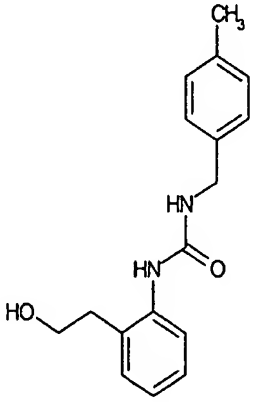
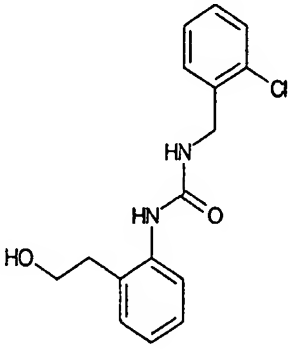
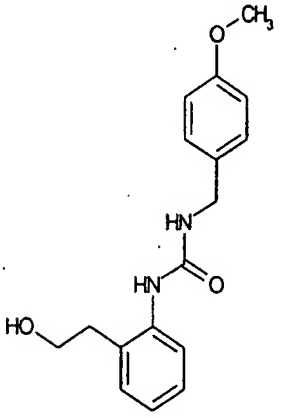
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
106		290,752		185-187	C
107		324,30535		173-175	B
108		324,30535		178-180	B
109		325,19703		214-216	B

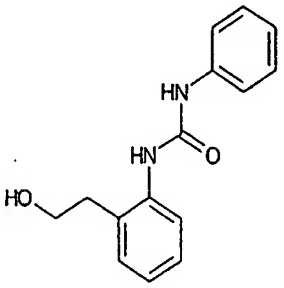
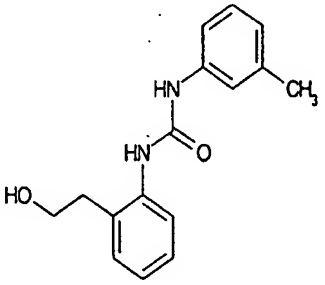
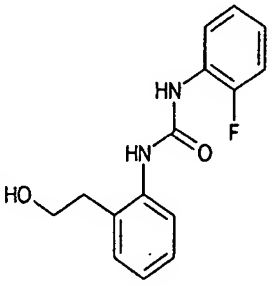
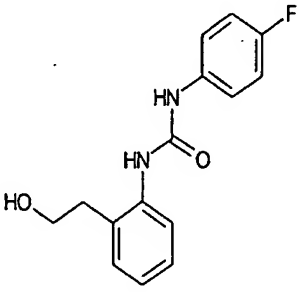
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
110		335,74953		178	C
111		319,29493		185	C
112		319,29493		183	C
113		335,74953		170	B
114		335,203		208	C

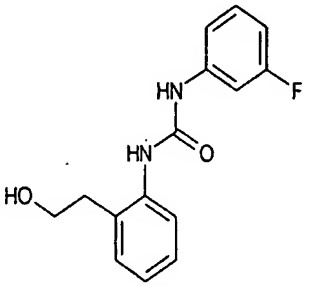
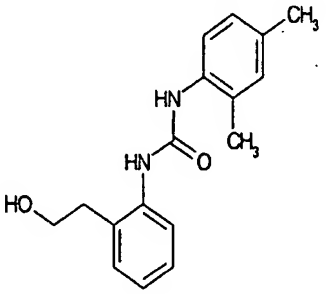
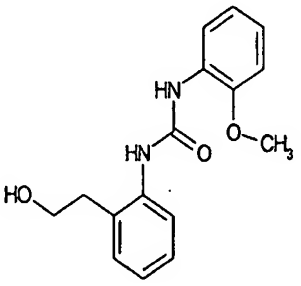
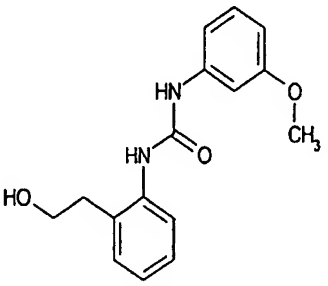
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
115		298,38824		243	C
116		284,36115		226	C
117		298,34461		177	C
118		314,34401		128	C

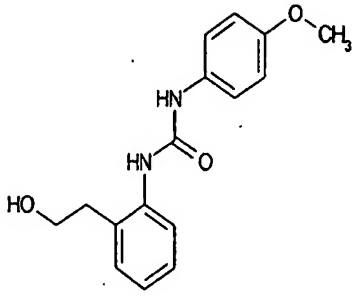
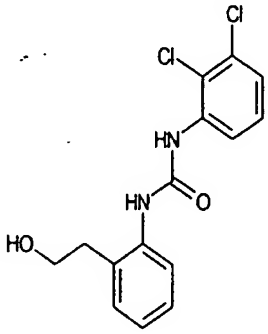
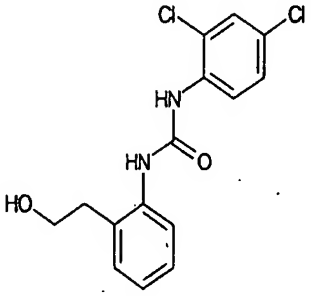
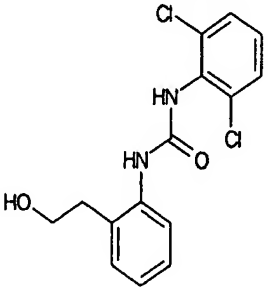
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
119		288,32449		141-143	C
120		288,32449		160-162	C
121		288,32449		165-167	C

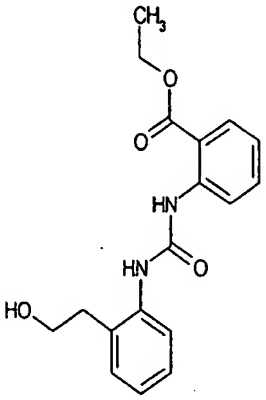
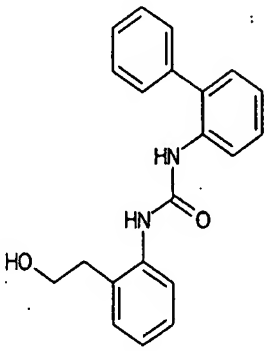
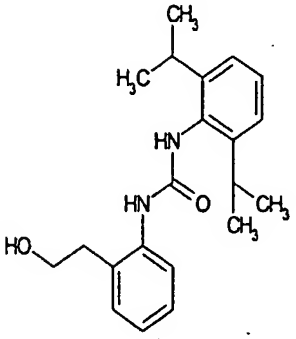
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
122		299,37582		187-188	C
123		284,36115		186-188	C
124		284,36115		148-150	C

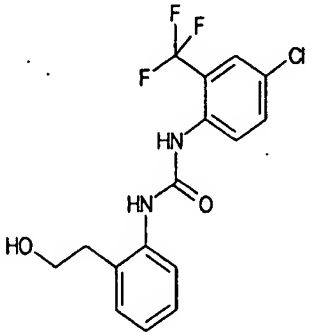
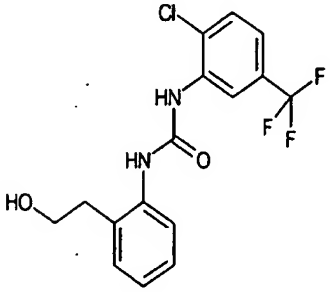
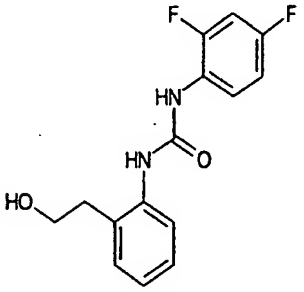
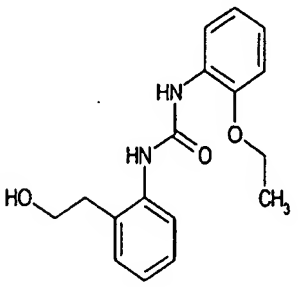
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
125		284,36115		181-183	C
126		304,77909		183-185	C
127		300,36055		175-177	C

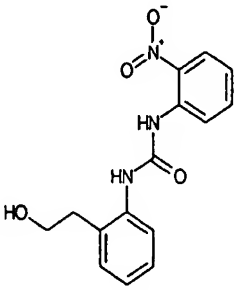
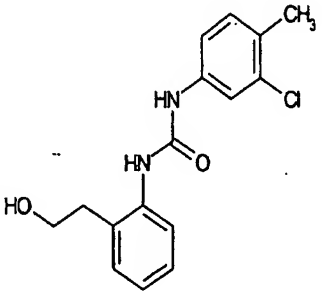
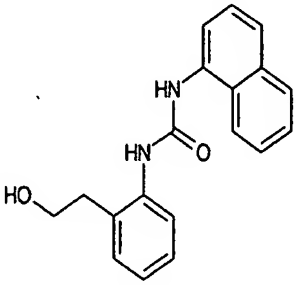
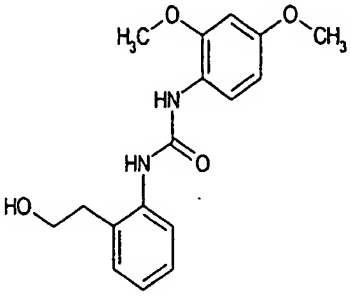
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
128		256,30697	385	ND	C
129		270,33406		186	C
130		274,2974	275	ND	C
131		274,2974		183	C

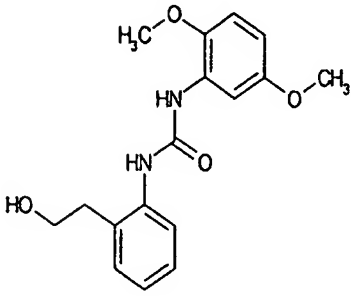
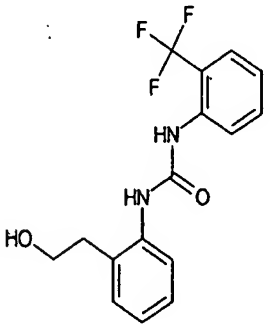
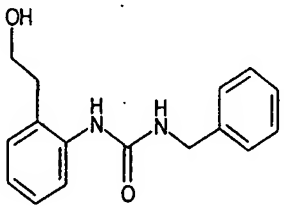
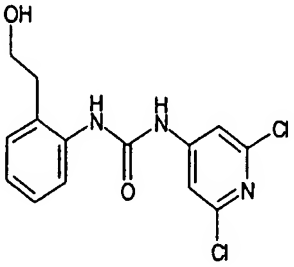
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
132		274,2974		166	C
133		284,36115		181	C
134		286,33346		154	C
135		286,33346		169	C

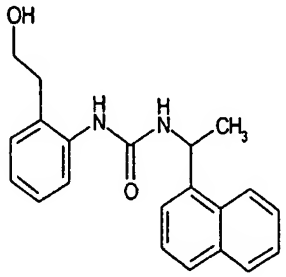
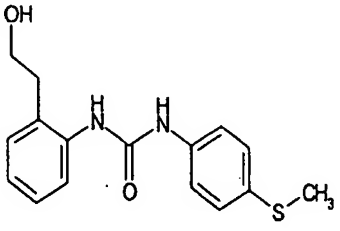
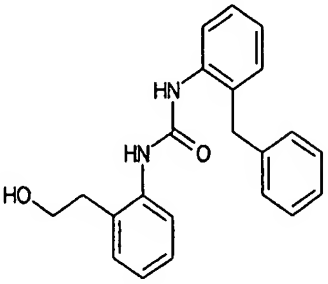
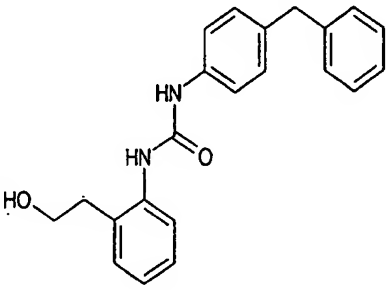
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
136		286,33346		186	C
137		325,19703	326	ND	C
138		325,19703	326	ND	C
139		325,19703	326	ND	C

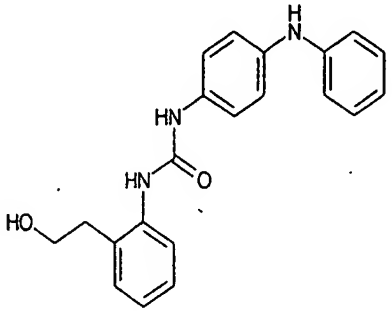
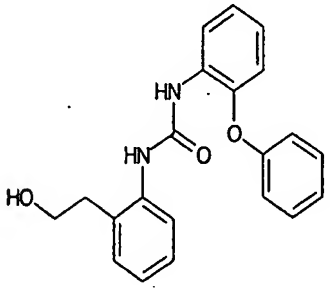
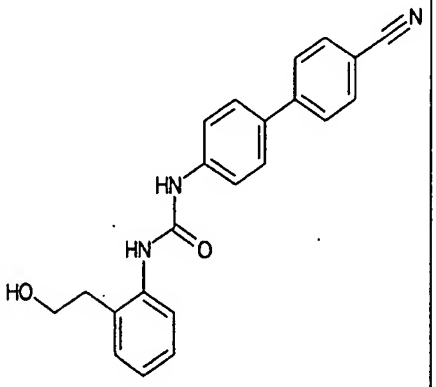
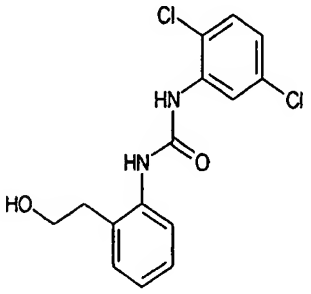
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
140		328,3711	329	ND	C
141		332,40575	333	ND	C
142		340,46951	344	ND	C

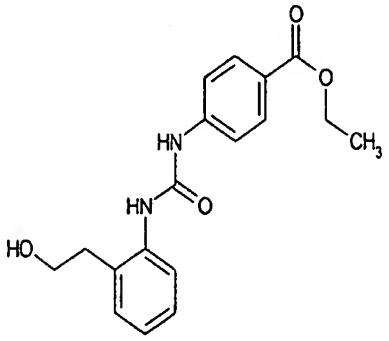
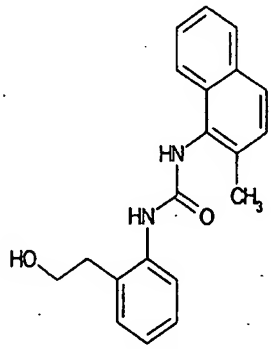
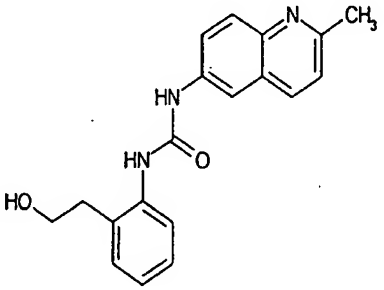
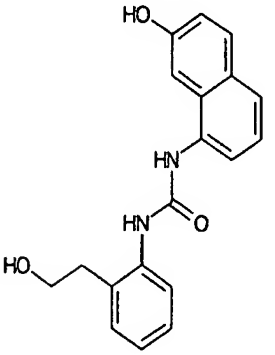
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
143		358,75038	359	ND	C
144		358,75038	359	ND	B
145		292,28783		174-176Z	C
146		300,36055		112-114Z	C

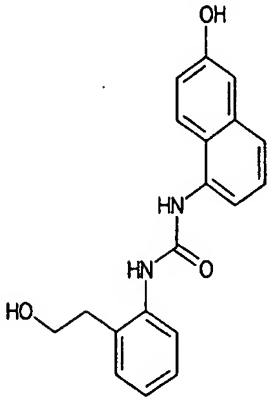
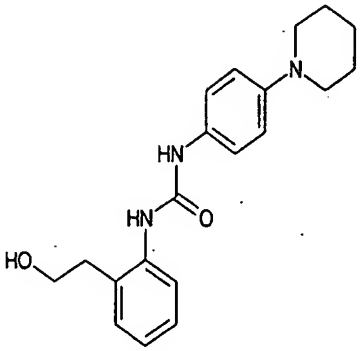
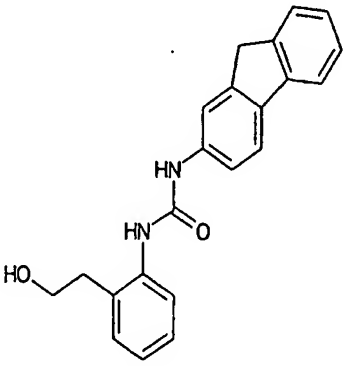
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
147		301,3045		112-114	C
148		304,77909		195-196	B
149		306,36751		188-191Z	C
150		316,35995		189-190	C

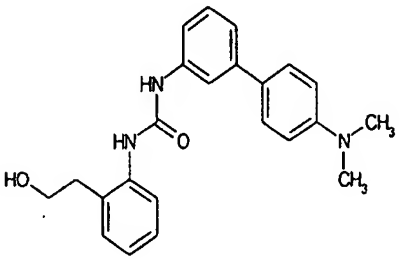
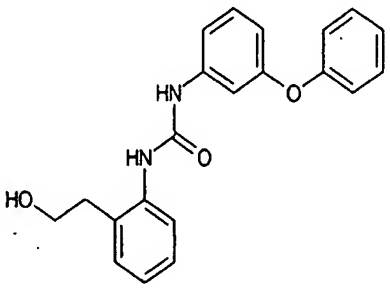
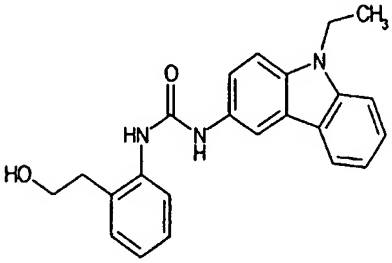
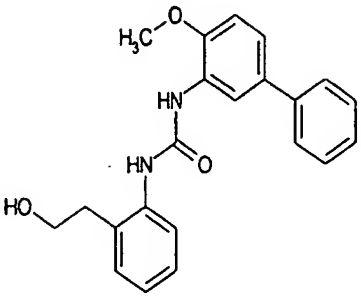
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
151		316,35995		157-158	C
152		324,30535		180-182	C
153		270,33406		149-150	C
154		326,18461		194	C

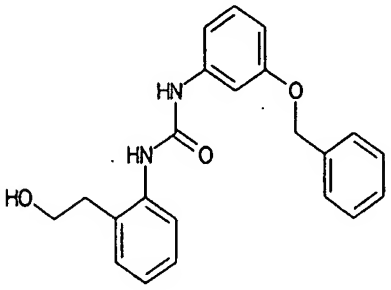
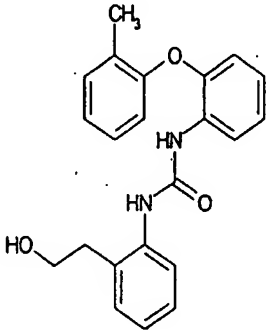
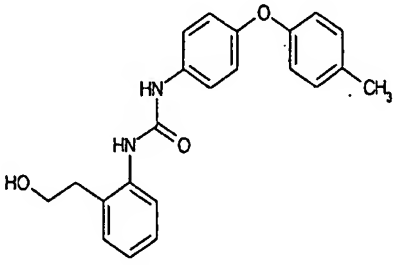
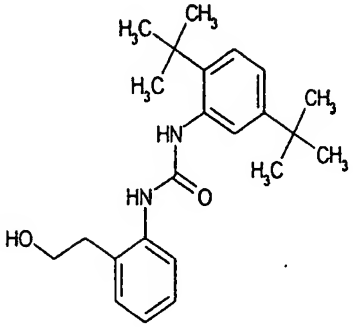
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
155		334,42169		176	C
156		302,39806		176-177	C
157		346,43284		162-164	C
158		346,43284		164-166	B

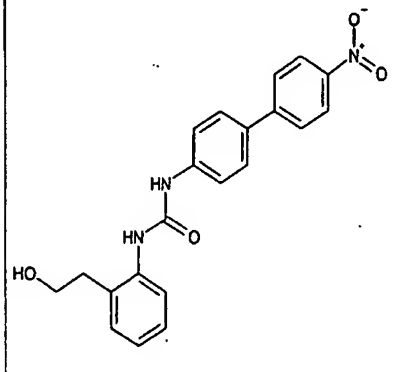
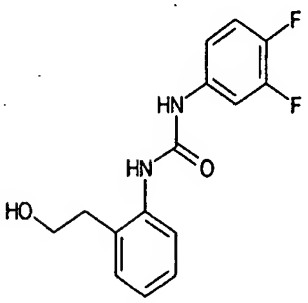
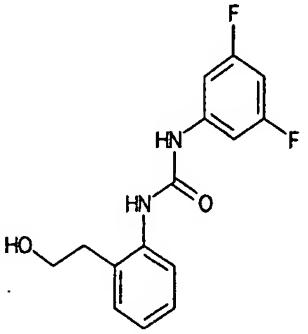
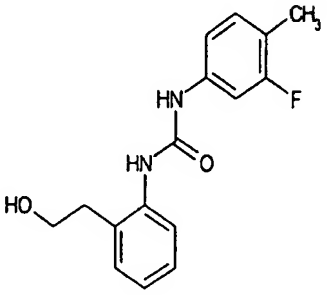
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
159		347,42042		150-151	C
160		348,40515		190-191	C
161		357,41563		213-215	C
162		325,19703	326	ND	C

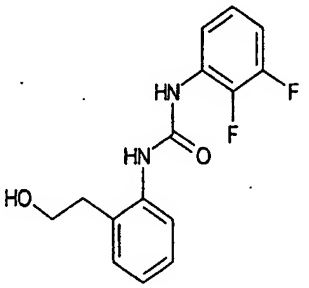
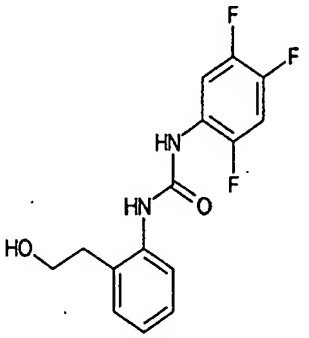
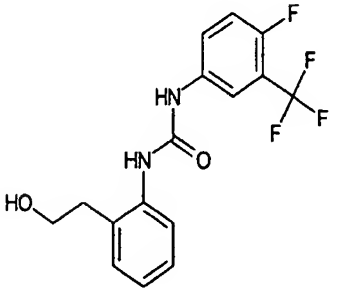
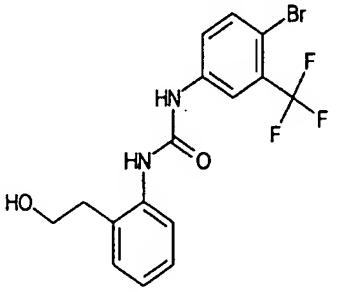
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
163		328,3711	326	ND	C
164		320,3946		204	C
165		321,38218		207	C
166		322,36691		212	C

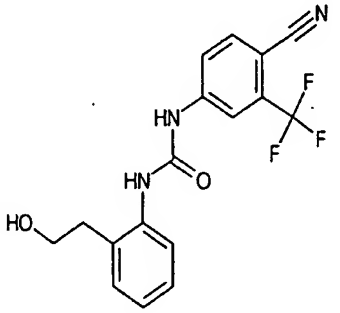
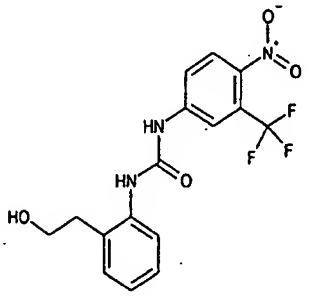
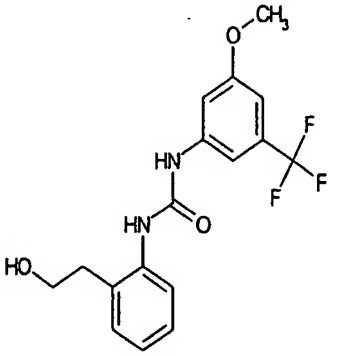
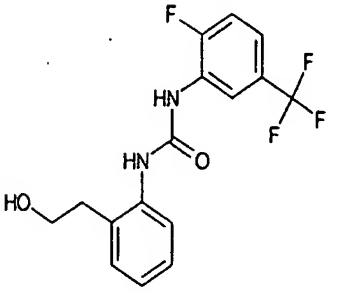
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
167		322,36691		188Z	C
168		339,44115		188	C
169		344,4169		>250	A

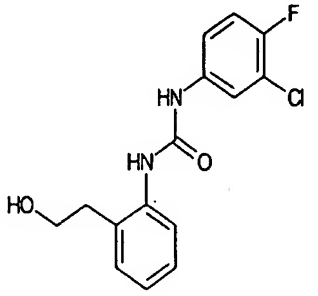
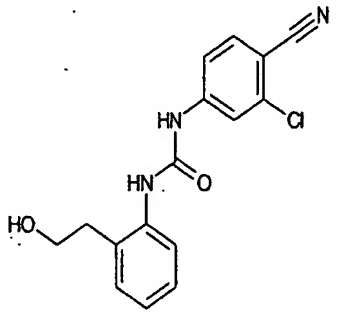
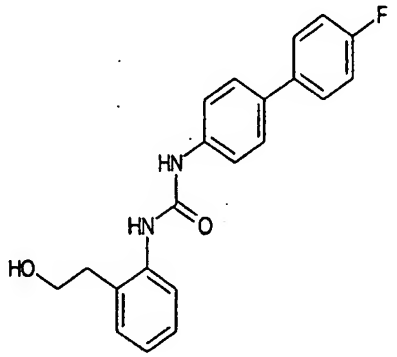
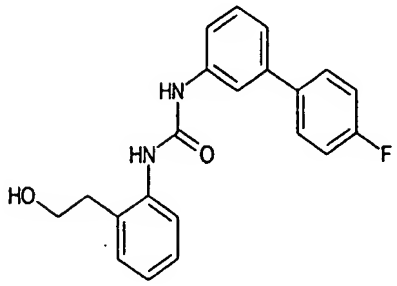
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
170		375,4746	326	ND	A
171		348,40515		145-146	A
172		373,45866		224-226	A
173		362,43224		178-180	B

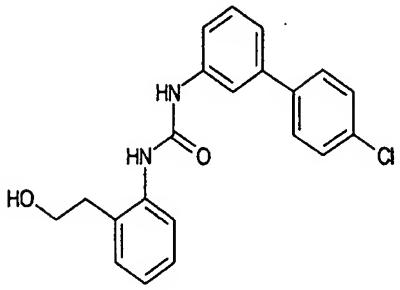
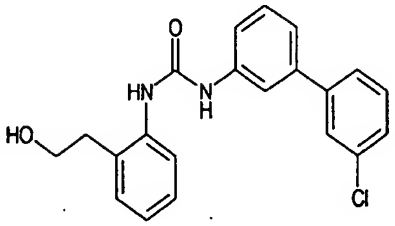
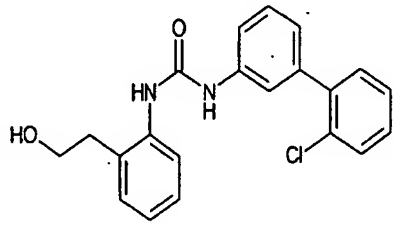
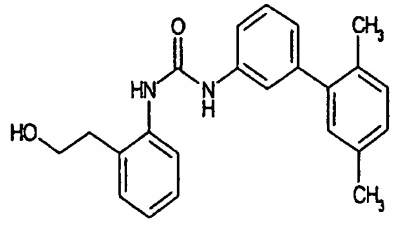
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
174		362,43224		146-148	A
175		362,43224		170-172	C
176		362,43224		164-168Z	A
177		368,52369	369	ND	C

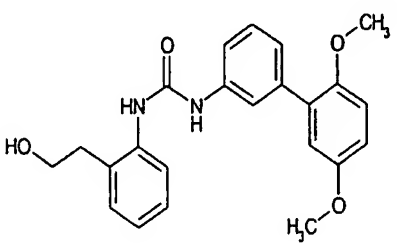
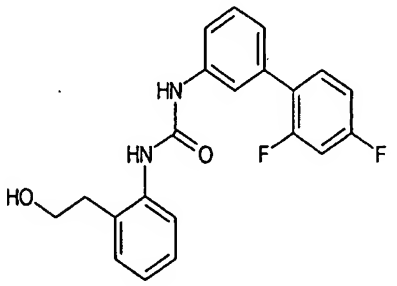
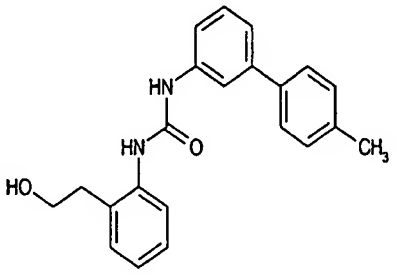
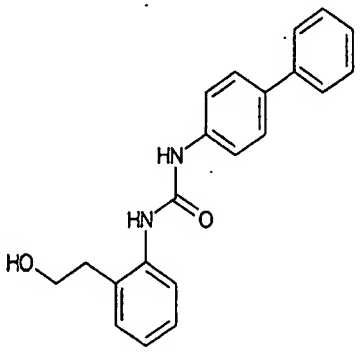
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
178		377,40328	378	ND	B
179		292,28783		162-164	C
180		292,28783		188-189	B
181		288,32449		184-186	C

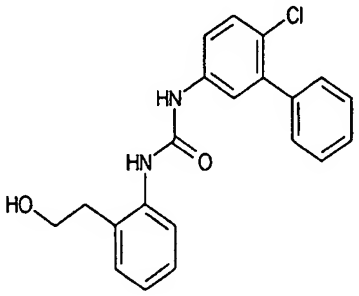
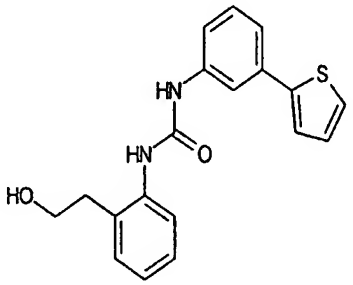
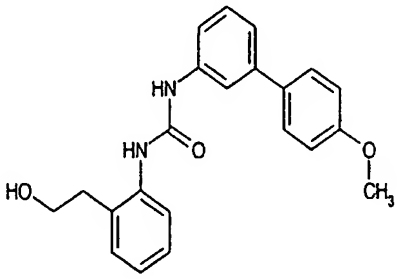
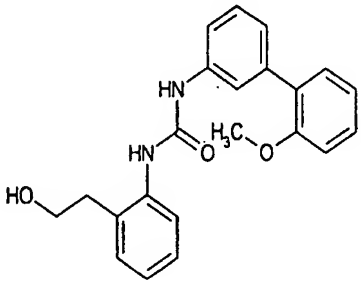
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
182		292,28783		159-161	C
183		310,27826		172-174	C
184		342,29578		158-161Z	A
185		403,20138		161-164	A

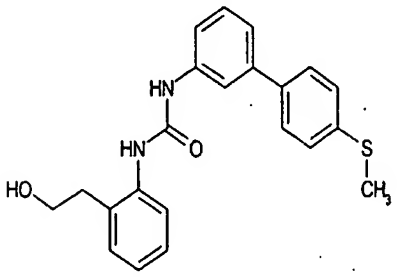
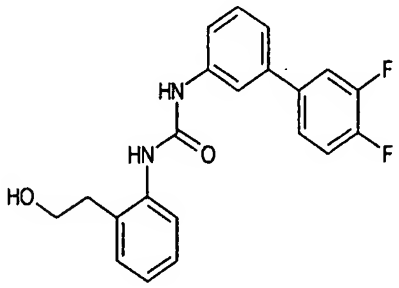
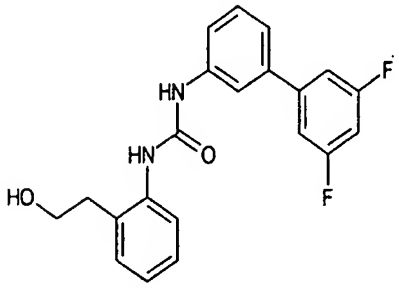
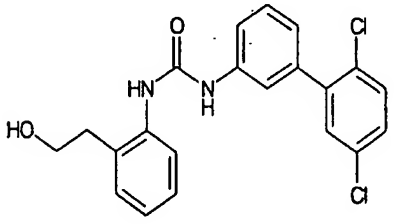
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
186		349,31523		171	A
187		369,30288		149-150	B
188		354,33184		161-162	A
189		342,29578		150-152	C

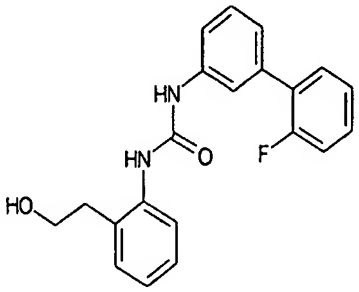
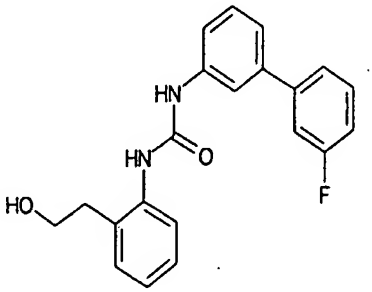
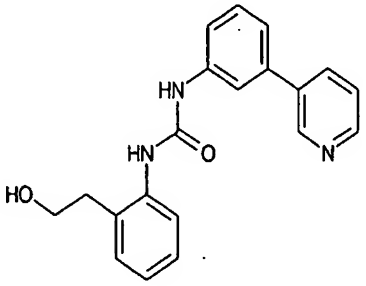
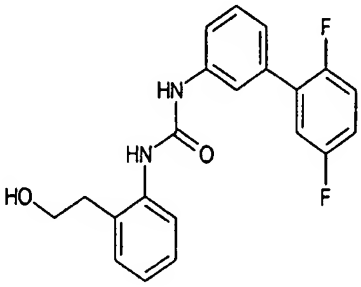
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
190		308,74243		193-194	B
191		315,76188		186-187	B
192		350,39618		197	B
193		350,39618	351	ND	A

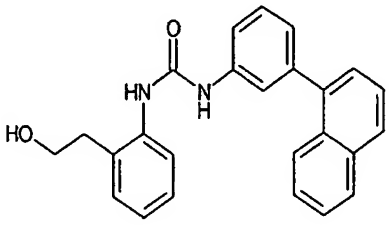
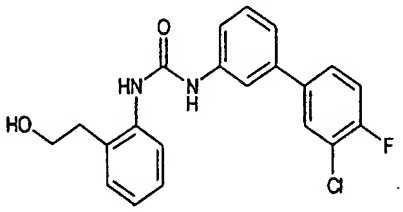
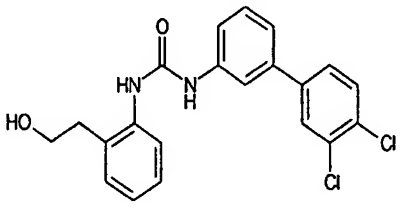
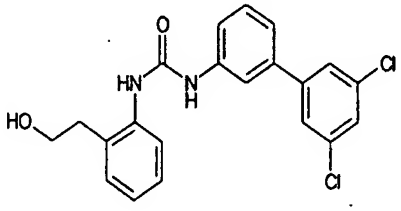
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
194		366,85078	367	ND	A
195		366,85078		175	A
196		366,85078		153	A
197		360,45993		167	A

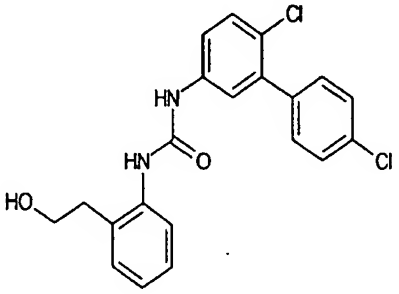
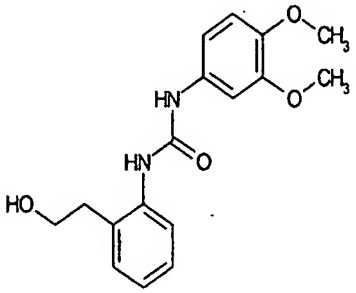
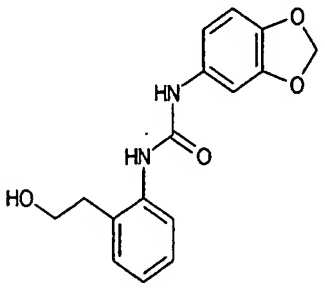
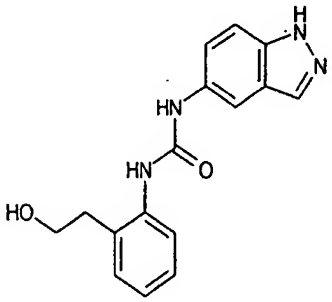
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
198		392,45873		170	B
199		368,38661		169	A
200		346,43284		178	A
201		332,40575		194	B

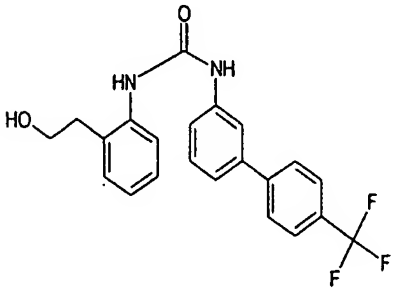
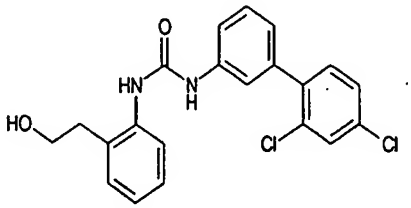
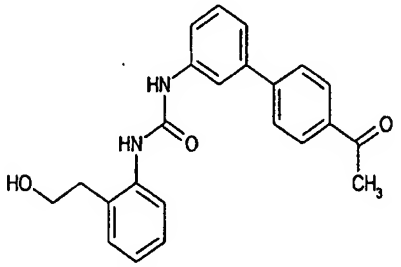
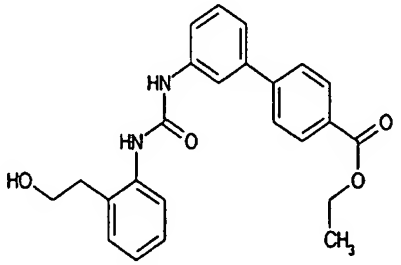
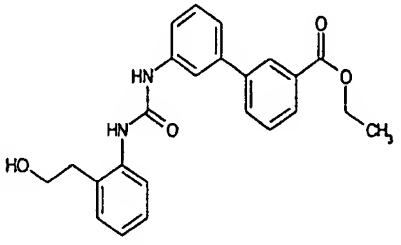
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
202		366,85078		185	B
203		338,43151		195	A
204		362,43224		166	A
205		362,43224		130	B

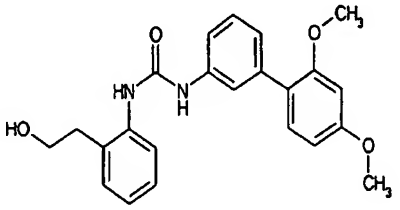
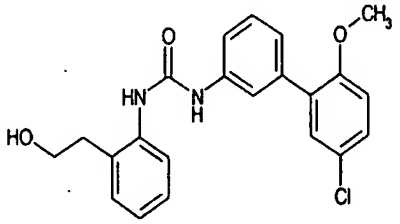
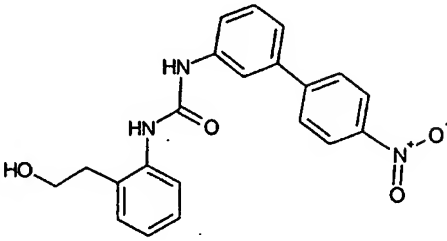
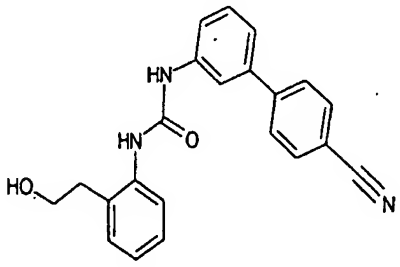
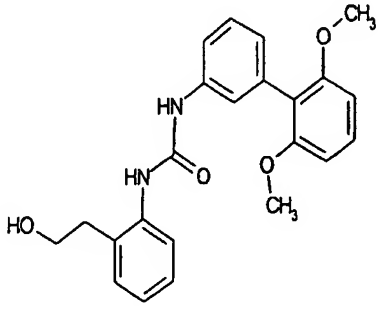
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
206		378,49684	379	191	A
207		368,38661	369	181	A
208		368,38661	369	169	A
209		401,29581		142	A

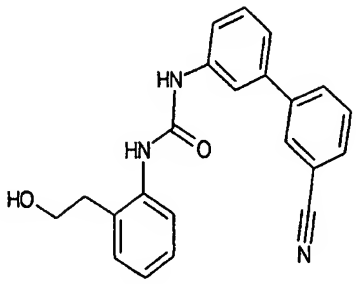
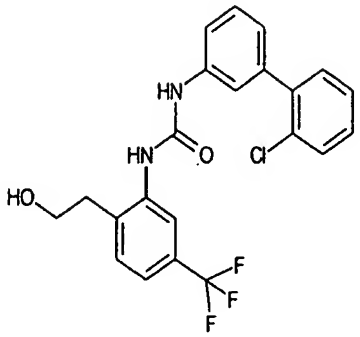
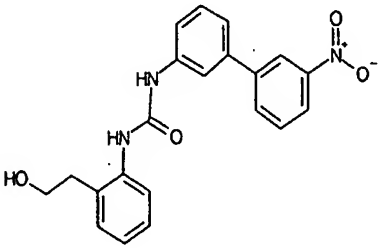
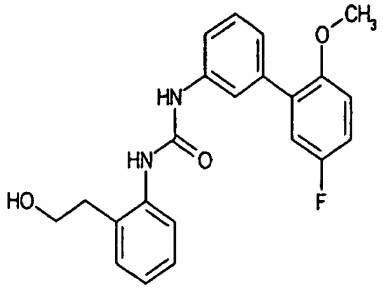
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
210		350,39618		171-172	A
211		350,39618		188	A
212		333,39333		178.9	C
213		368,38661	369	150	A

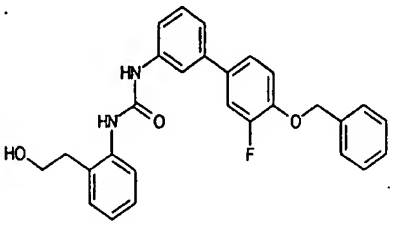
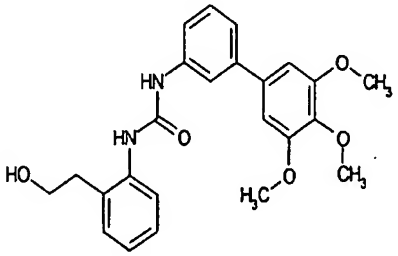
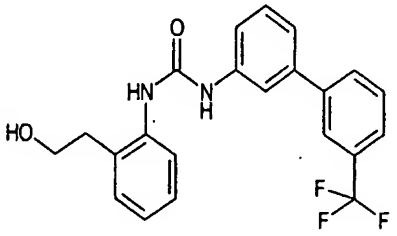
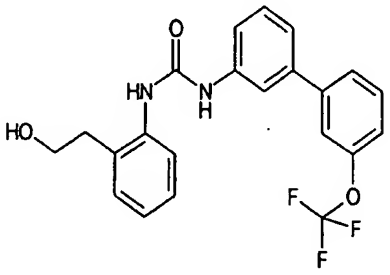
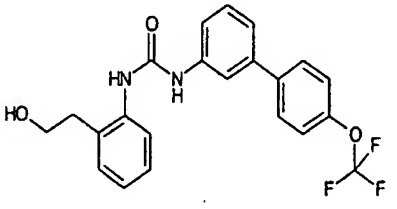
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
214		382,46629		113	A
215		384,84121		176	A
216		401,29581		180	A
217		401,29581		184	A

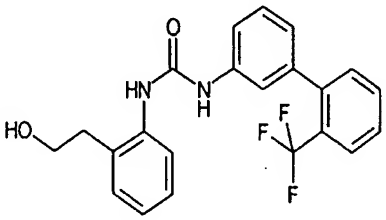
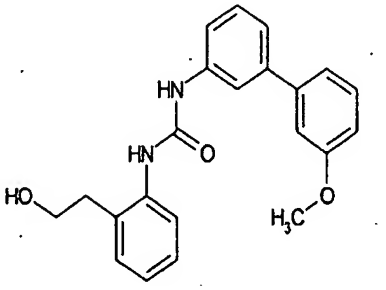
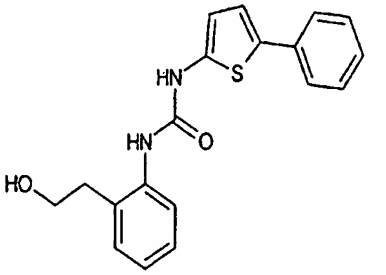
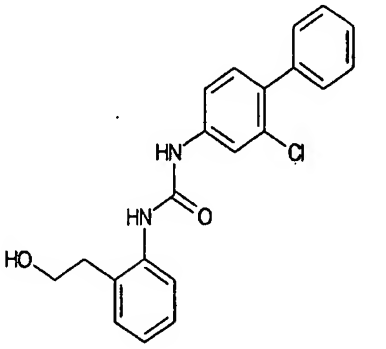
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
218		401,29581		170-172	A
219		316,35995		186-187	C
220		300,31692		183-184	C
221		296,33152		234-236	C

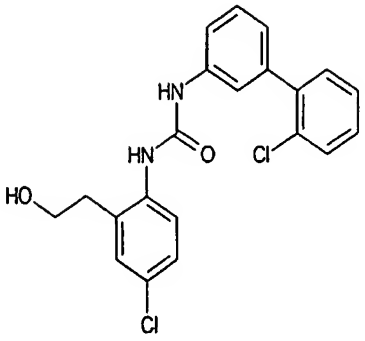
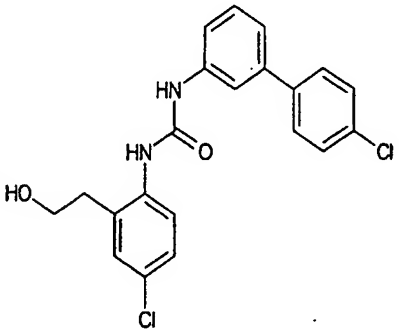
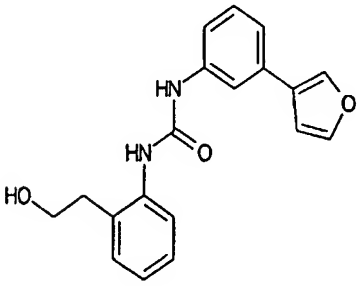
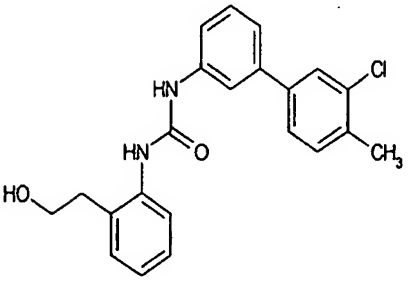
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
222		400,40413		198	A
223		401,29581		166	A
224		374,44339		205	A
225		404,46988		196	A
226		404,46988		133	A

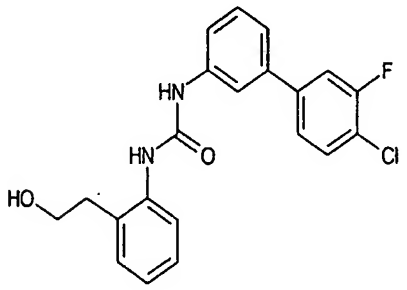
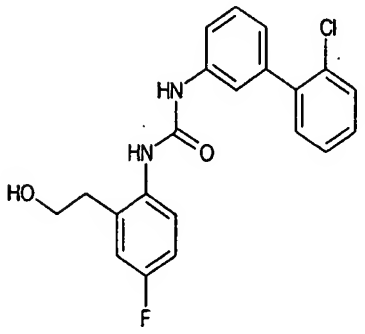
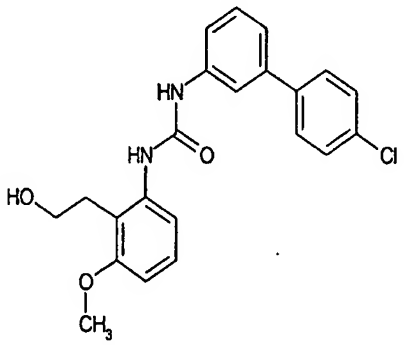
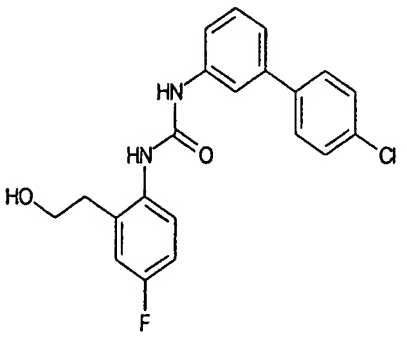
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
227		392,45873		141-143	A
228		396,87727		126-129	A
229		377,40328		197-198	A
230		357,41563		180-182	A
231		392,45873		180-181	C

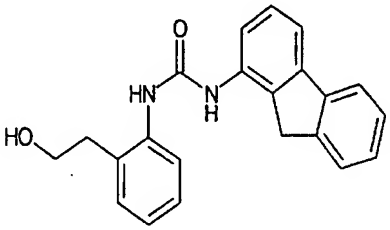
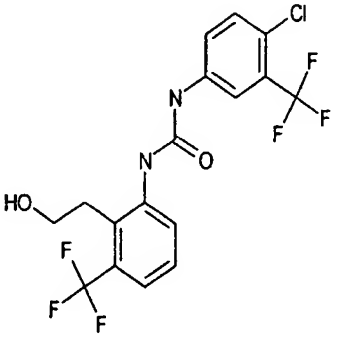
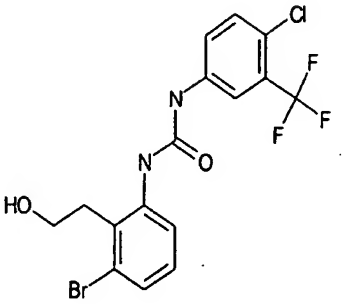
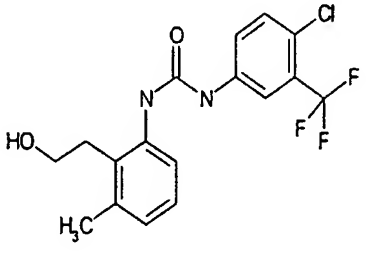
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
232		357,41563		186-187	A
233		434,84916		185-187	B
234		377,40328		188	A
235		380,42267		158-160	A

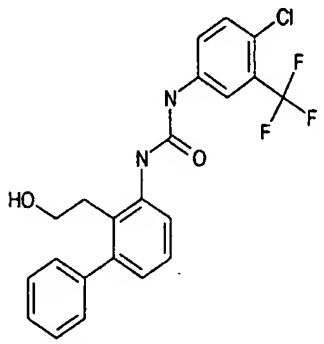
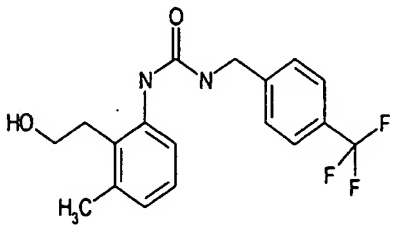
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
236		456,52145		181-182	A
237		422,48522		81-83	B
238		400,40413		180	A
239		416,40353		166	A
240		416,40353		184	A

Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
241		400,40413		153	A
242		362,43224		163	A
243		338,43151		159	A
244		366,85078		178	B

Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
245		401,29581		191-193	B
246		401,29581		209-211	C
247		322,36691		190	A
248		380,87787		194	A

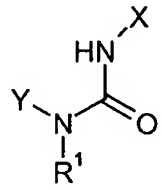
Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
249		384,84121		180	A
250		384,84121	369	177	B
251		396,87727	385	195	A
252		384,84121	397	187	B

Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
253		344,4169		182-183	A
254		426,7488	427	201	B
255		437,6464	438	209	A
256		372,7775	373	201	A

Ex. No	MOLSTRUCTURE	MW	M+1	melting point	hVR1 class
257		434,8492	435	173	B
258		352,3595	353	213	A

CLAIMS

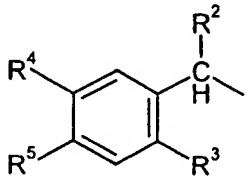
(1) An urea derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:



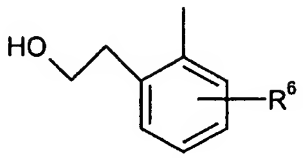
(I)

wherein

Y is



(I-i) or



(I-ii)

;

X is C_{1-6} alkyl substituted by phenyl or naphthyl (wherein said phenyl and naphthyl are optionally substituted by R^{11}, R^{12} and R^{13}), aryl or heterocyclic ring ,

wherein said aryl and heterocyclic ring are optionally substituted by R^{11}, R^{12} and R^{13} and are are selected from the group consisting of phenyl, naphthyl, pyridyl, carbazolyl, fluorenyl, thienyl, pyrimidyl, benzodioxolyl, indazolyl, and quinolyl,

in which R^{11}, R^{12} and R^{13} independently represent hydrogen, halogen, C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyl, nitro, cyano, C_{1-6} alkoxy, hydroxy, piperidino, furyl, thienyl, benzyloxy, anilino, naphthyl, C_{1-6} alkylcarbamoyl, carbamoyl, carboxyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} alkoxycarbonyl, benzyl, phenoxy, C_{1-6} alkyl substituted phenoxy, pyridyl, halogen substituted phenoxy, C_{1-6} alkylthio, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, hydroxy

substituted C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyloxy, or phenyl optionally substituted by one to three substituents,

in which the substituents are each different or identical and selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, pyridyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyl, nitro, cyano, benzyloxy, thienyl, C_{1-6}alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylthio, di(C_{1-6} alkyl)amino, and C_{1-6} alkylamino, mono, di, or tri halogen substituted C_{1-6} alkyloxy;

R^1 is hydrogen,

R^2 is hydrogen,

R^3 is hydrogen,

or

R^2 and R^3 together form $-(CH_2)_m-$ (wherein m represents 1, 2, 3 or 4),

or

R^1 and R^3 together form $-(CH_2)_n-$ (wherein n represents 1, 2, or 3);

R^4 is hydrogen, halogen, C_{1-6} alkoxy, hydroxy, C_{1-6} alkoxy substituted benzyloxy, sulfamoyl, C_{1-6} alkylsulfamoyl, di(C_{1-6} alkyl)sulfamoyl, di(C_{1-6} alkyl)amino C_{1-6} alkylene sulfamoyl, hydroxy C_{1-6} alkyl piperazinosulfonyl, C_{1-6} alkylsulfonylamino, nitro, amino, C_{1-6} alkanoylamino, C_{1-6} alkoxyC_{1-6} alkyleneoxy,

R^5 is hydrogen, halogen, C_{1-6} alkoxy, hydroxy, C_{1-6} alkoxy substituted benzyloxy, sulfamoyl, C_{1-6} alkylsulfamoyl, di(C_{1-6} alkyl)sulfamoyl, di(C_{1-6} alkyl)amino C_{1-6} alkylene sulfamoyl, hydroxy C_{1-6} alkyl piperazinosulfonyl, C_{1-6} alkylsulfonylamino, nitro, amino, C_{1-6} alkanoylamino, C_{1-6} alkoxyC_{1-6} alkyleneoxy,

or

R^4 and R^5 together form $-O-(CH_2)-O-$; and

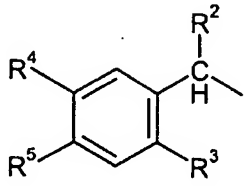
R^6 is hydrogen, halogen, C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyl, nitro, cyano, C_{1-6} alkoxy, hydroxy, C_{1-6} alkylcarbamoyl, carbamoyl, carboxyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino,

C_{1-6} alkoxycarbonyl, phenyl, benzyl, phenoxy, halogen substituted phenoxy, C_{1-6} alkylthio, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, hydroxy substituted C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkoxy.

(2) The urea derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

Y is



(I-i)

;

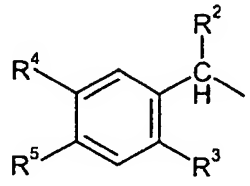
X is phenyl optionally substituted by R^{11}, R^{12} and R^{13}, phenyl C_{1-6} alkyl (wherein said phenyl is optionally substituted by R^{11}, R^{12} and R^{13}), or naphthyl optionally substituted by R^{11}, R^{12} and R^{13},

in which R^{11}, R^{12} and R^{13} independently represent hydrogen, halogen, C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyl, nitro, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, phenoxy, C_{1-6} alkylthio, or C_{1-6} alkanoyl.

(3) The urea derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

Y is



(I-i)

;

R^1 is hydrogen;

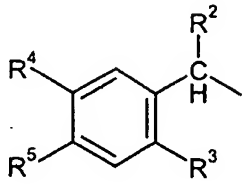
R^2 is hydrogen; and

R^3 is hydrogen.

(4) The urea derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

Y is


(I-i)
;

X is phenyl optionally substituted by R^{11}, R^{12} and R^{13}, phenyl C_{1-6} alkyl (wherein said phenyl is optionally substituted by R^{11}, R^{12} and R^{13}), or naphthyl optionally substituted by R^{11}, R^{12} and R^{13},

in which R^{11}, R^{12} and R^{13} independently represent hydrogen, halogen, C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyl, nitro, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, phenoxy, C_{1-6} alkylthio, or C_{1-6} alkanoyl.

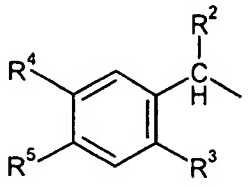
R^1 is hydrogen; and

R^2 and R^3 together form $-(CH_2)_m-$ (wherein m represents 1, 2, 3 or 4).

(5) The urea derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

Y is


(I-i)
;

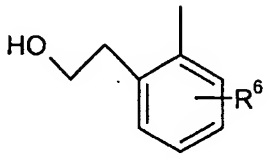
R^1 and R^3 together form $-(CH_2)_n-$ (wherein n represents 1, 2, or 3); and

R^2 is hydrogen.

(6) The urea derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

Y is



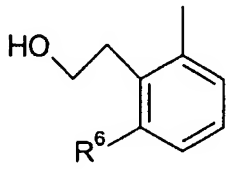
(I-ii) ;

R^6 is hydrogen, halogen, C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyl, phenyl or C_{1-6} alkoxy.

(7) The urea derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

Y is



(I-ii-a) ;

X is C_{1-6} alkyl substituted by phenyl or naphthyl (wherein said phenyl and naphthyl are optionally substituted by R^{11}, R^{12} and R^{13}), aryl or heterocyclic ring ,

wherein said aryl and heterocyclic ring are optionally substituted by R^{11}, R^{12} and R^{13} and are selected from the group consisting of phenyl, naphthyl, pyridyl, carbazolyl, fluorenyl, thienyl, benzodioxolyl, indazolyl, and quinolyl,

in which R^{11}, R^{12} and R^{13} independently represent hydrogen, halogen, C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyl, nitro, cyano, C_{1-6} alkoxy, hydroxy, piperidino, furyl, thienyl, benzyloxy, anilino, naphthyl, di(C_{1-6} alkyl)amino, C_{1-6} alkoxycarbonyl, benzyl, phenoxy, C_{1-6} alkyl substituted phenoxy, pyridyl, halogen substituted phenoxy, C_{1-6} alkylthio, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, hydroxy substituted C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyloxy,

or phenyl optionally substituted by one to three substituents, in which the substituents are each different or identical and selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, pyridyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyl, nitro, cyano, benzyloxy, thienyl, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylthio, di(C_{1-6} alkyl)amino, C_{1-6} alkylamino, and mono-, di- or tri- halogen substituted C_{1-6} alkyloxy; and

R^6 is hydrogen, halogen, C_{1-6} alkyl, mono-, di-, or tri- halogen substituted C_{1-6} alkyl, phenyl or C_{1-6} alkoxy.

(8) The urea derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1, wherein said urea derivative of the formula (I) is selected from the group consisting of:

N-(4-hydroxy-3-methoxybenzyl)-N'-(4-isopropylphenyl)urea;
N-(4-hydroxy-3-methoxybenzyl)-N'-(1-naphthyl)urea;
N-(3,4-dichlorophenyl)-N'-(4-hydroxy-3-methoxybenzyl)urea;
N-(3-chloro-4-methylphenyl)-N'-(4-hydroxy-3 methoxybenzyl)urea;
N-(4-hydroxy-3-methoxybenzyl)-N'-(4-phenoxyphenyl)urea;
N-[2-chloro-5-(trifluoromethyl)phenyl]-N'-(4-hydroxy-3-methoxybenzyl)urea;
N-(3-chlorophenyl)-N'-(4-hydroxy-3-methoxybenzyl)urea;

N-(4-chlorophenyl)-N'-(4-hydroxy-3-methoxybenzyl)urea;
N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-hydroxy-3-methoxybenzyl)urea;
N-(4'-chloro-1,1'-biphenyl-3-yl)-N'-(4-hydroxy-3-metoxybenzyl)urea;
N-[2-(2-hydroxyethyl)phenyl]-N'-[4'-(methylsulfanyl)-1,1'-biphenyl-3-yl]urea;
N-[2-(2-hydroxyethyl)phenyl]-N'-(4'-nitro-1,1'-biphenyl-3-yl)urea;
N-(4'-acetyl-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
Ethyl3'-[({[2-(2hydroxyethyl)phenyl]amino}carbonyl)amino]
-1,1'-biphenyl-4-carboxylate;
N-[2-(2-hydroxyethyl)phenyl]-N'-[2'-(trifluoromethyl)-1,1'-biphenyl-3-yl]urea;
N-(2'-chloro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-[2-(2-hydroxyethyl)phenyl]-N'-[3-(1-naphthyl)phenyl]urea;
N-[2-(2-hydroxyethyl)phenyl]-N'-[4'-(trifluoromethyl)-1,1'-biphenyl-3-yl]urea;
N-(4',6-dichloro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-(2',5'-dichloro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-(2',4'-dichloro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-(3',4'-difluoro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-(4'-fluoro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-[2-(2-hydroxyethyl)phenyl]-N'-(3'-nitro-1,1'-biphenyl-3-yl)urea;
N-[4'-(benzyloxy)-3'-fluoro-1,1'-biphenyl-3-yl]-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-(4'-chloro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-(2',5'-dimethyl-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-[2-(2-hydroxyethyl)phenyl]-N'-[4'-(trifluoromethoxy)-1,1'-biphenyl-3-yl]urea;
N-(4'-chloro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)-3-methoxy-phenyl]urea;
N-(3'-fluoro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;

N-(3'-chloro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea;
N-(2',5'-difluoro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea; and
N-(3'-chloro-4'-fluoro-1,1'-biphenyl-3-yl)-N'-[2-(2-hydroxyethyl)phenyl]urea.

(9) An urea derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claims 1 for the treatment and/or prophylaxis of diseases.

(10) A medicament comprising the urea derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

(11) The medicament as claimed in claim 10, further comprising one or more pharmaceutically acceptable excipients.

(12) The medicament as claimed in claim 10, wherein the urea derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is a VR1 antagonist.

(13) The medicament as claimed in claim 10 for treatment and/or prophylaxis of a disease selected from the group consisting of urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence and inflammatory disorders.

(14) An agent to treat or prevent urological disorder; comprising the urea derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

(15) An agent to treat or prevent of urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain,

neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence and inflammatory disorders; comprising the urea derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

(16) A method for treating or preventing disorder or disease associated with VR1 activity in a human or animal subject, comprising administering to said subject a therapeutically effective amount of the urea derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1.

(17) The method of claim 16, wherein said disorder or disease is a urological disorder or disease.

(18) The method of claim 16, wherein said disorder or disease is selected from the group consisting of urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence and inflammatory disorders.

(19) The method of claim 16, wherein said urea derivative , its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is administered with one or more pharmaceutically acceptable excipients.

(20) Use of the urea derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 in the preparation of a medicament.

(21) Use of urea derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 in the

preparation of a medicament for treating or preventing disorder or disease associated with VR1 activity.

(22) The use of claim 21, wherein said disorder or disease is urological disorder or disease.

(23) The use of claim 21, wherein said disorder or disease is selected from the group consisting of urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence and inflammatory disorders.

(24) The use of claim 21, wherein said urea derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is formulated with one or more pharmaceutically acceptable excipients.

(25) Process for controlling urological disorders in humans and animals by administrating of a VR1 antagonisticly effective amount of at least one compound as claimed in claim 1.

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(74) Common Representative: **BAYER AKTIENGESELLSCHAFT**; 51368 Leverkusen (DE).

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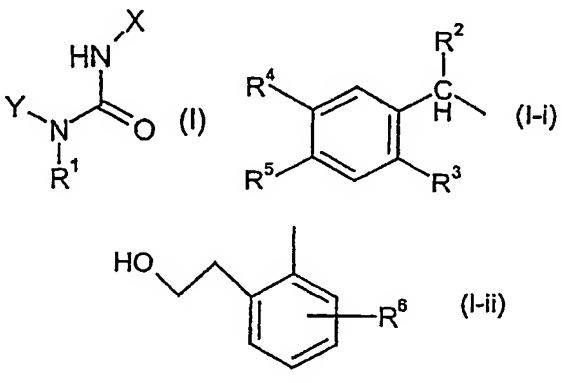
[Continued on next page]

(54) Title: UREA DERIVATIVES AS VR1- ANTAGONISTS



(57) Abstract: This invention relates to urea derivatives of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof: (I) wherein Y is R^1- R^6 and X have the same meanings given in the description, which is useful as an active ingredient of pharmaceutical preparations. The urea derivatives of the present invention has an excellent activity as VR1 antagonist and useful for the prophylaxis and treatment of urge urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence and/or inflammatory disorders.

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(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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C07D223/16 A61K31/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 50387 A (KIM HEE DOO ;OH UHTAEK (KR); PARK YOUNG HO (KR); SUH YOUNG GER (KR) 31 August 2000 (2000-08-31) cited in the application claim 1 ---	1-3,8-25
Y	KLOPMAN G & LI J-Y: "Quantitative structure-agonist activity relationship of capsaicin analogues" JOURNAL OF COMPUTER-AIDED MOLECULAR DESIGN, vol. 9, no. 3, 1995, pages 283-294, XP009008828 example 54 --- -/--	1-3,8-25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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International Application No
PCT/EP 02/14216

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 16318 A (JEONG YEON SU ;JOO YUNG HYUP (KR); KIM HEE DOO (KR); KIM SUN YOUNG) 28 February 2002 (2002-02-28) claim 1 ---	1-3,8-25
P,X	WO 02 072536 A (WYMAN PAUL ADRIAN ;GLAXOSMITHKLINE (GB); THOMPSON MERVYN (GB); SMI) 19 September 2002 (2002-09-19) claim 1 ---	1-3,8-25
P,X	DI MARZO V ET AL.: "A Structure/Activity Relationship Study on Arvanil, an Endocannabinoid and Vanilloid Hybrid" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 300, no. 3, 2002, pages 984-991, XP001145825 examples 0-1987 ---	1-3,8-25
L,E	WO 03 014064 A (BAYER AG ;FREITAG JOACHIM (DE); MEIER HEINRICH (DE); LOWINGER TIMO) 20 February 2003 (2003-02-20) examples 6,7,30,31,33,42,43,51; table 1 examples 52,66,71,78; table 1 example 20; table 4 -----	1-3,8-25

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 16-19 and 25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-7 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 2, 8-25 (all in part), 3 (entirely)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-7 (in part)

Present claims 1-7 relate to an extremely large number of possible compounds. For instance, a well-known compound such as dibenzylurea (CAS RN 1466-67-7) falls within the scope of the general formula according to the first invention. Support within the meaning of Article 6 PCT is to be found, however, for only a very small proportion of the compounds claimed. As a result, the claims so lack support that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely, insofar as invention 1 is concerned, those parts relating to the compounds of formula (I) where the phenyl ring of group Y bears at one meta position an oxygen, chlorine or fluorine atom, and at the para position a hydrogen, carbon, chlorine or fluorine atom.

Despite this limitation, a very high number of potentially relevant documents (over 150) were found, so that it is impossible to determine the scope of protection which might legitimately be sought by the claims. Therefore, the documents selected to be cited in the search report were limited to documents relating to compounds having the same therapeutic activity as the claimed compounds.

Should the applicant decide to pay the other search fees, then he is informed of the fact that a similar limitation might be necessary in order to allow a search for the other inventions. For instance, regarding inventions 2 and 3, a lack of clarity may arise from the fact that specific meanings have been given to R2 and R3 or R1 and R3, but the meanings of R1 in the former case in of R2 in the latter are left open.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1, 2, 8-25 (all in part), 3 (entirely)

   Compounds of formula (I) wherein Y is a group of formula (I-i), R1-R3 all being hydrogen, pharmaceutical compositions containing them and use thereof in the treatment of diseases associated with VR1 activity.

2. Claims: 1, 2, 9-25 (all in part), 4 (entirely)

   Compounds of formula (I) wherein Y is a group of formula (I-i), R2 and R3 forming together a group -(CH2)m-, pharmaceutical compositions containing them and use thereof in the treatment of diseases associated with VR1 activity.

3. Claims: 1, 2, 9-25 (all in part), 5 (entirely)

   Compounds of formula (I) wherein Y is a group of formula (I-i), R1 and R3 forming together a group -(CH2)n-, pharmaceutical compositions containing them and use thereof in the treatment of diseases associated with VR1 activity.

4. Claims: 1, 2, 8-25 (all in part), 6, 7 (entirely)

   Compounds of formula (I) wherein Y is a group of formula (I-ii), pharmaceutical compositions containing them and use thereof in the treatment of diseases associated with VR1 activity.

INTERNATIONAL SEARCH REPORT

formation on patent family members

Inte—ional Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0050387 A	31-08-2000	AU 2697600 A	14-09-2000
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		EP 1154989 A1	21-11-2001
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		KR 2001014495 A	26-02-2001
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